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Prediction of Outcome After Abdominal Aortic Aneurysm Rupture

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Doctor of Medicine

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In memory of my father

Table of Contents

Abstract

This thesis aims to examine the validity of existing tools recommended for outcome prediction after abdominal aortic aneurysm (AAA) rupture and to design and validate a novel risk scoring instrument. It also aims to examine the utility of novel predictive variables. Finally, it examines the functional outcomes achieved by survivors of aneurysm rupture.

Existing risk models and predictive variables for outcome were validated on a retrospective cohort of consecutive patients with ruptured AAA. These data were also used to design a novel prognostic index for outcome prediction. A prospective cohort of consecutive patients was used to further validate these scoring systems, examine novel prognostic variables and determine functional outcome.

Existing risk scoring instruments for patients with ruptured AAA lack validity. Analysis of preoperative variables in patients with ruptured AAA shows that absolute surgical futility cannot be predicted. However, in-hospital hypotension (<90mmHg), reduced Glasgow Coma Scale (<15) and anaemia (<9g/dL) are associated with perioperative death. When these risk factors are equally weighted and combined to create a novel risk scoring instrument (Edinburgh Ruptured Aneurysm Score-ERAS), three discriminatory tiers of risk are demonstrable. The validity of this risk instrument is confirmed on prospective data. Examination of novel perioperative prognostic variables shows that elevated cardiac troponin I, with or without clinically apparent cardiac dysfunction, is predictive of death after ruptured AAA repair. However, although ruptured AAA are associated with an early elevation in inflammatory biomarkers, these do not appear to confer additional prognostic value. Furthermore, for the first time, prospective study shows that patients who survive ruptured AAA repair achieve a good recovery in terms of functional outcome within six months of operation.

Surgical futility cannot be predicted prior to operation in patients with AAA. However, the ERAS shows potential as a preoperative prognostic index in patients with ruptured AAA.

Declaration

I declare that this thesis has been composed by me. The work is my own and based on research undertaken in the Division of Clinical & Surgical Sciences (Surgery), School of Clinical Sciences and Community Health, University of Edinburgh from August 2002 to December 2004. This work has not been submitted for any other degree or professional qualification.

Andrew Tambyraja

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1.Introduction

There is no disease more conducive to clinical humility than aneurysm of the aorta.

Sir William Osler

1.1. Overview

This thesis examines the outcomes of patients with ruptured abdominal aortic aneurysm (AAA). As the incidence of this condition continues to increase, survival has remained essentially unchanged over the past 30-years [1]. It has been suggested that the only means by which to improve perioperative mortality after aneurysm rupture may be to operate only on patients with reasonable operative risk.

The majority of vascular surgeons in the UK employ a selective policy when faced with patients with ruptured AAA [2]. Thereby, clinicians must frequently make the decision whether to palliate or to operate on a given patient. To date this remains a largely subjective decision. There is an array of reports on risk scoring and outcome prediction aimed at informing such decision-making. However, all of these tools lack adequate validation and their use cannot be robustly supported in clinical practice. Furthermore, there remain many misconceptions concerning variables that may influence outcome after ruptured AAA that are largely based on anecdotal evidence and inadequate knowledge.

In this introductory chapter, the relevant clinical and pathophysiological background and previous published literature in the field will be discussed.

1.2. Abdominal aortic aneurysm

The normal diameter of the aorta varies with age, sex and bodyweight [3]. It decreases in size as it leaves the thorax and enters the abdomen, tapering to its iliac bifurcation. However, the infrarenal aorta enlarges progressively with age. An aortic aneurysm may be defined as a permanent localised dilatation of at least a 50% increase in diameter compared to the expected normal diameter of the aorta [4]. If the maximum normal diameter of the aorta is considered to be 2.1cm, aneurysmal dilatation is said to occur when the diameter exceeds 3.0cm.

The abdominal aorta comprises of three histologically distinct tissue layers: an intima, media, and adventitia. True aneurysms represent a dilatation of all three layers of the vessel wall. The abdominal aorta is the most commonly affected artery and accounts for 90% of all aneurysms. Of these, 95% will originate below the level of the renal arteries. The aortic arch, thoracic aorta and thoracoabdominal aorta are involved in approximately 10% of aneurysms [5].

The morphology or shape of aneurysms may be classified as saccular or fusiform, although this description represents a continuous spectrum. Saccular aneurysms only affect a small portion of the aortic circumference while fusiform lesions involve the entire circumference of the vessel.

1.3. Epidemiology

Ruptured abdominal aortic aneurysm (AAA) accounts for around 10 000 deaths each year in the United Kingdom[6]. This represents a similar number of deaths caused by gastric, oesophageal and prostatic malignancies [7]. Over the past 20-years, hospital based admissions and mortality from AAA in the UK have continued to rise [8,9]. These trends have also been reported in Europe, Australia and the USA [10-12].

Knowledge of the prevalence of AAA has implications for the planning and organisation of health-care resources. In determining the prevalence of AAA, the frequently asymptomatic nature of the disease is a major confounding factor. Data on prevalence stem from four sources: autopsy surveys, routine mortality and hospital in-patient statistics and population-screening surveys. It should be noted that all of these sources have their limitations and potential for bias; screening surveys offer, potentially, the most accurate estimate of prevalence.

The prevalence of screen detected AAA in men in England is reported to be between 1.3 and 12.7 per cent [13]. This variation is accounted for by differing criteria for the definition of AAA and the age group screened. If the criterion of aortic diameter >29mm is used as the definition for AAA, the prevalence ranges between 2.9 and 7.6 per cent [13]. The prevalence of AAA amongst women in this country, though less well documented, is much lower and is reported to be around 1.3 per cent [14]. These figures are in keeping with data from other European and North American series [15,16]. Interestingly, data from autopsy based surveys yield similar results. The prevalence

of AAA at autopsy in the UK has been reported at 2.3 per cent in men and 1.6 per cent in women. [17]

Scottish hospital records data have reported the overall incidence of asymptomatic AAA to be around 63.6 cases per 100 000 per year [18]. Similar studies from North America, Australia and Western Europe report incidences of between 3.0 and 117.2 per 100 000 people per year [15,19,20]. Variation in these figures is attributable to the differing data sources utilised: hospital records, death certificates and autopsy reports [13]. However, all studies report a consistent increase with time in the age-adjusted incidence of AAA. Such a finding may be accounted for in part by increasing AAA-related hospital admissions due to greater awareness, improved methods of diagnosis and a lower threshold for surgical intervention. Nevertheless, it is suggested that a real increase in AAA incidence has occurred at a time when other cardiovascular diseases have been declining [8].

The reported incidence of ruptured AAA ranges from 1 to 21 per 100 000 people per year [13]. Here too, a steady increase in incidence has also been identified. This finding is unrelated to population age flux, as the age-standardised mortality has also risen. Although it is possible that increased awareness has led to an increase in the citation of AAA as a cause of death, it is felt that there has been a true increase in the incidence of aneurysm rupture.

Recent work has examined trends in hospital related admissions and AAA related mortality in Scotland. Between 1981 and 2000, 42.3 per cent of the 10 822 deaths

from aortic aneurysm in Scotland were attributed to the abdominal aorta. Age-adjusted mortality rates for AAA increased 2.6-fold from 2.62 deaths per 100 000 in 1981 to 6.82 per 100 000 in 2000 (Fig. 1.3.2) [8]. Unlike previous studies that have considered trends in AAA during the period of introduction of ultrasonography and computed tomography, there have been no significant advances in the diagnosis of aortic aneurysm over the past 10–15 years to account for these increases. Hospital admissions for AAA also rose threefold, with increases in both elective admissions (from 3.05 to 7.80 per 100 000) and emergency admissions (from 7.44 to 11.23 per 100 000).

Figure 1.3.1. 3-Dimensional reconstruction of intact AAA

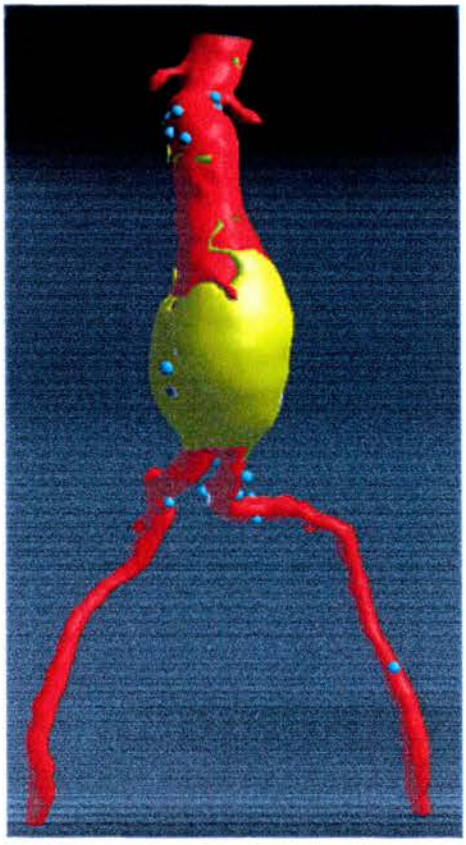
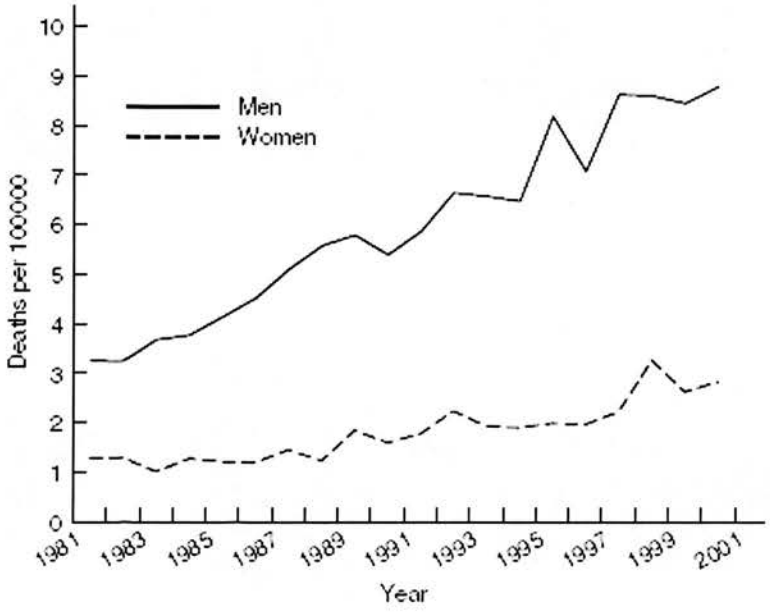


Fig. 1.3.2. Age-adjusted mortality rates for abdominal aortic aneurysm in men and women in Scotland between 1981 and 2000 [8]



There were consistently more emergency admissions than elective, although the proportion of elective admissions did increase with time. Surgical workload increased dramatically during the study period, from 130 operations for AAA in 1981 to 528 in 2000. It was also noted that there was a large increase in the proportion of patients over 75 years undergoing emergency surgery [8].

These data imply that the incidence of AAA has increased over the past 20 years in Scotland. This is unlikely to be due to changes in detection and diagnosis, or ageing of the population. The increase in incidence of both elective and emergency admission suggests that a genuine and persistent rise in the incidence of AAA has occurred.

1.4. Aetiology and risk factors

The cause of aneurysms remains unclear. Historically, aneurysmal change was thought to be underpinned by atherosclerosis. However, because of histological and epidemiological differences it is now recognised that atherosclerosis is a coexistent secondary phenomenon and the majority of AAA (90%) are thought to represent a degenerative or non-specific process [21].

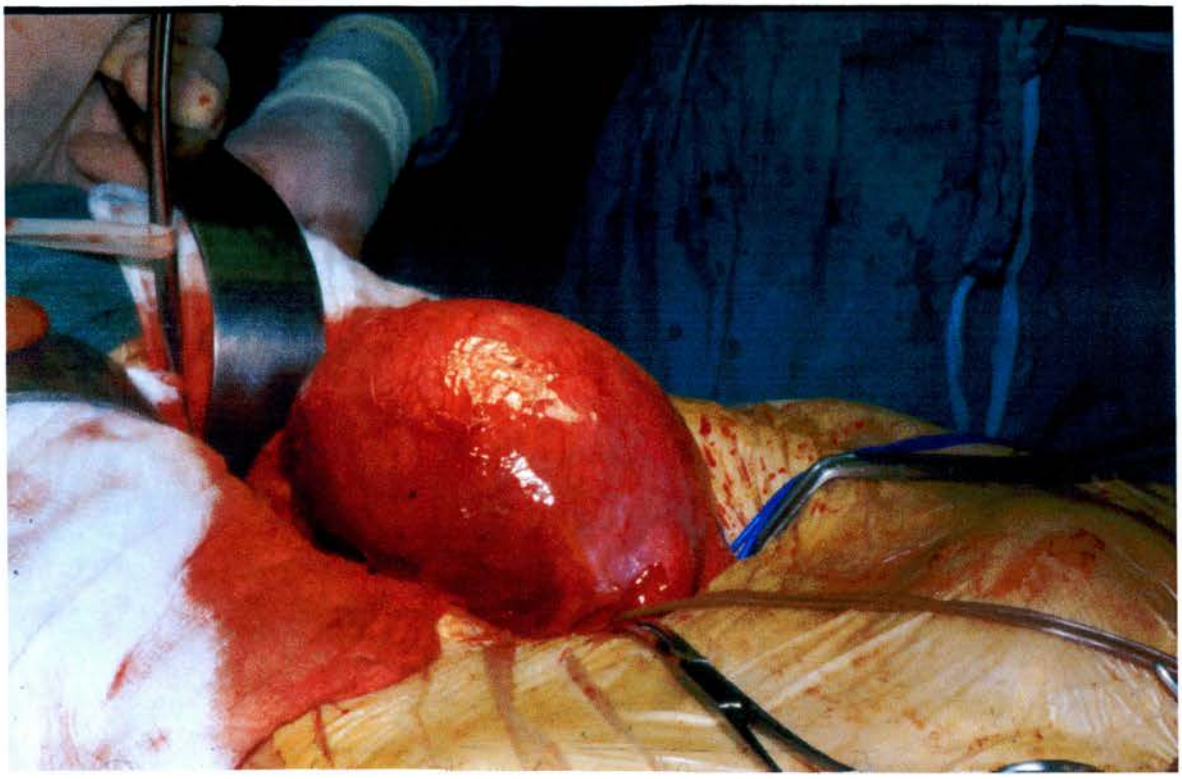
Abdominal aortic aneurysms exhibit familial clustering. This raises the possibility of both genetic and environmental aetiological factors. Genes encoding for type III collagen, matrix metalloproteinases and protease inhibitors and plasminogen activator inhibitor have all been reported to play some role in AAA development or expansion [22,23]. However, no specific genes have been convincingly implicated to date and it is inferred that susceptibility to the development of AAA is an irreversible process with multiple genetic and environmental risk factors. Genetic influences are attributed to a few gene polymorphisms with large effects [22].

North American and European data suggests that there is a four-fold increase in risk of having an AAA for the brother of a patient having an AAA [24,25]. Familial abdominal aortic aneurysms are more common when the index case is female and rupture is said to occur at a younger age and more often than with sporadic aneurysms [26,27].

Established independent risk factors for AAA included male gender, age, hypertension, hyperlipidaemia and smoking [28-30]. In particular, the relationship between tobacco use and AAA development is striking. Aneurysms are four-times

more prevalent amongst smokers than non-smokers and the comparative relative risks of chronic cigarette smokers developing an AAA are three-fold greater than their risk of developing coronary artery disease [29,31]. For these reasons, it is thought that smoking is the foremost environmental risk factor for aneurysm development and growth.

Figure 1.4.1. Large asymptomatic AAA



1.5. Pathology

Abdominal aortic aneuryms are characterised histologically by destruction of elastin and collagen in the tunica media and tunica adventitia, smooth muscle cell apotosis with thinning of the medial wall, infiltration of lymphocytes and macrophages, and neovascularization [32]. Four pathological mechanisms are thought to play central roles in AAA development: Proteolyis of connective tissue, inflammation, biomechanical stress and genetic influences [33].

Proteolysis:

Macrophage and aortic smooth muscle cell derived matrix metalloproteinases (MMPs) and other proteases are secreted into the extracellular matrix and are integral to aneurysm formation [34, 35]. Though MMPs are expressed and active during normal physiological aortic remodeling, they mediate degradation of elastin and collagen within the aortic media and internal lamina in AAA pathogenesis [36]. A shift in the balance between MMPs and their inhibitors moves away from normal remodeling activity towards pathological elastin and collagen degradation. Factors initiating and propagating proteolyis in the aorta remain unclear [37].

Inflammation

Transmural lymphocyte and macrophage infiltration is a histological characteristic of AAA [32]. An inflammatory cytokine cascade released by these cells is thought to stimulate protease activation. The chemotactic trigger responsible for this cellular migration remains uncertain, although it has been proposed that aortic elastin

degradation products, interstitial collagen or oxidized low-density lipoprotein, may be an antigenic and chemotactic stimulus for macrophages [37].

Other factors stimulating a vascular inflammatory response include *Chlamydia pneumoniae, Treponema pallidum,* Cytomegalovirus, and Herpes Simplex Virus. It is hypothesized that these agents may initiate the proteolytic cascade resulting in matrix degradation [38, 39]. Interestingly, *Chlamydia pneumoniae* has been demonstrated in as many as 55% of aneurysms and antibody titers have been directly correlated with aneurysm expansion, while doxycycline treatment has resulted in reduced rates of aneurysm expansion [40-42].

Biomechanics

The aortic wall contains smooth muscle, elastin, and collagen arranged in concentric layers in order to withstand arterial pressure. Elastin is the principal load-bearing element in the aorta while collagen provides tensile strength and helps maintain the structural integrity of the vascular wall [43]. The normal aorta displays a reduction in the elastin to collagen ratio as it passes from the thorax into the abdomen [37]. Thus, the abdominal aorta has less elastin and as a consequence, less load-bearing potential than the aortic arch.

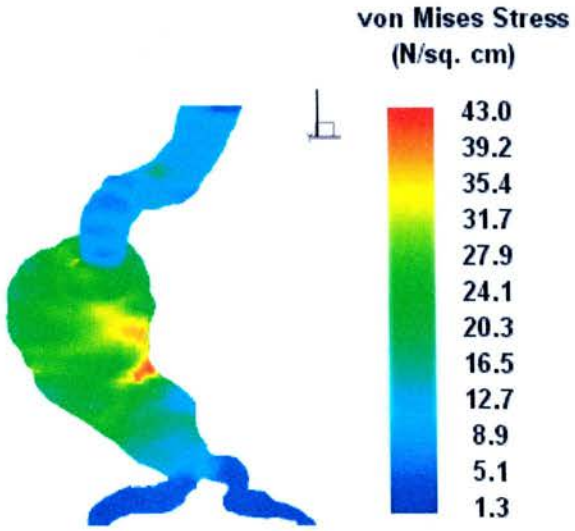
Matrix metalloproteinase-9 expression and activity is increased in the abdominal aorta compared with aortic arch and thoracic aorta. Activation of these proteases is also thought to be brought about by the disruption of normal laminar flow seen in the infra renal aorta [44]. Furthermore, the attenuation of the vasa vasorum in the infrarenal

aorta is proposed to contribute to relative hypoxia of the vessel stimulating MMP activity. These factors are all thought to contribute to the predisposition of the infrarenal aorta to develop aneurysmal change [37].

Genetics

As already discussed, though multifactorial genetic influences are involved in AAA development, the polymorphisms responsible for aneurysm pathogenesis remain elusive. Similarly, the phenotypic expression of these traits is uncertain. It is proposed that an abnormality of the primary structures of elastin and collagen or a mutation, directly or indirectly, affecting protease and protease-inhibitor activity are implicated [23].

Figure 1.5.1. Biomechanical stress distribution in a ruptured AAA



1.6. Biology of AAA rupture

The concept that aortic rupture occurs when wall stress exceeds the tensile strength of the aneurysm wall is now recognised to be an oversimplification of the mechanisms at play. This is reinforced by the observation that even small aneuryms may rupture [45]. Recent work has proposed that the tensile strength of aneurysmal aortic wall is heterogeneous. It is felt that enhanced enzyme activity within the aortic wall results in focal areas of weakness or 'hotspots' that are susceptible to rupture at relatively low wall stress [46].

It should be noted that although elastin degradation is an important characteristic in aortic dilatation, it is the proteolytic degradation of collagen, predominantly in the adventitia, that predisposes to aortic rupture. This may be considered the final common pathway in the progression to rupture [47]. The role of matrixmetalloproteinases in AAA evolution has already been alluded to. However, they are thought to play a role in aneurysm rupture too. While MMP-2 is implicated in the expansion of small AAA, MMP-9 activity is closely related to large aneurysms. Matrixmetalloproteinase-9 levels are reported to be six fold greater in ruptured compared to intact AAA [48]. It has also been observed that MMP-9 levels are much higher at the site of aneurysm rupture when compared to a distant, intact area of AAA wall [49]. These findings lend weight to the hypothesis that areas of increased MMP activity result in focal hotspots of aneurysm wall that are vulnerable to rupture[46].

The role of the immune response in AAA rupture remains controversial. Though its effect may culminate in promoting connective tissue breakdown and smooth muscle apoptosis, it may also exert a reparative influence mediated by anti-inflammatory

cytokines that inhibit macrophage activation and MMP expression [47,50]. Further confounding evidence stems from the observation of rapid AAA growth and even rupture in patients receiving chemotherapy regimens [51]. Similar findings have also been noted in patients who receive immunosuppressive regimens following organ transplantation [52]. Recent work on Natural Killer (NK) T-cells has shown that patients with an AAA have significantly higher percentages of peripheral blood NK cells when compared to both arteriopaths and normal controls [53]. Furthermore Natural Killer cells from patients with an AAA display increased cytotoxicity towards both an NK-sensitive target cell line and human aortic smooth muscle cells [53]. Increased NK cytotoxicity could be a contributing factor in the generation or potentiation of inflammation in patients with an AAA.

Intraluminal thrombus develops in the majority of AAA and it has been suggested that it plays a part in aneurysm rupture. Again, the precise relationship between thrombus and aneurysm rupture is uncertain. Patients with ruptured AAA display evidence of acute haemorrhage within mural thrombus and this may be a causal relationship [54]. Alternatively, an extensive interface of thrombus reduces oxygen delivery from the true lumen to the aortic wall [55]. This may result in inflammation with associated proteolysis and a reduction in local wall tensile strength predisposing to rupture [47]. The constituents of thrombus also include inflammatory cells that are capable of mediating proteolytic enzyme release and activation [56]. This is supported by the observation of elevated levels of plasmin at the thrombus-aortic interface [57].

Relative hypoxia of the aortic wall may also compromise the integrity of extracellular matrix synthesis [47]. Cell culture work on aortic endothelial cells has shown that hypoxic conditions result in reduced collagen synthesis [59]. Moreover, the collagen synthesised is abnormal due to the need for oxygenation in the hydroxylation of proline [60].

The biology of aneurysm rupture remains far less certain than the pathogenesis of aneurysms themselves. The concepts that have been discussed are likely to interact in the common pathway that culminates in AAA rupture. These influences may be amenable to therapeutic manipulation as a means of slowing or arresting the progress towards rupture.

Figure 1.6.1. Macroscopic pathological specimen of ruptured AAA

1.7. Cardiac injury

Coexistent coronary artery disease (CAD) in patients with peripheral vascular disease is well documented. It is reported that perioperative myocardial ischemia occurs in 20% to 40% of patients undergoing vascular surgery; of whom 50% develop adverse events [60]. In the Cleveland Clinic study, hemodynamically significant CAD was demonstrated in more than a third of patients with AAA [61]. Cardiac injury may be precipitated by the insults of anaesthesia related hypotension, blood loss, fluid shifts, aortic cross-clamping and ischaemia-reperfusion injury. In the context of ruptured aneurysms, death and postoperative morbidity in patients who undergo technically successful repair of a ruptured aneurysm is commonly attributed to the development of myocardial infarction [62]. However, the detection of clinically signficiant perioperative cardiac injury and its prognostic implications remain unclear.

Cardiac events have been traditionally diagnosed on clinical, electrocardiographic (ECG) and biochemical criteria. The diagnosis of acute myocardial infarction as defined by the World Health organisation and recently revised by the Joint European Society of Cardiology/American College of Cardiology committee is shown in Table 1.7.1 [63].

Table 1.7.1. Criteria of the World Health Organization and the Joint European Society of Cardiology/American College of Cardiology

World Health Organization criteria for MI

Definite acute MI

1. Definite ECG or
2. Symptoms typical or atypical or inadequately described, together with probable ECG or abnormal enzymes or
3. Symptoms typical with abnormal enzymes with ischaemic or non-codable ECG or ECG not available or
4. Fatal case, whether sudden or not, with naked eye appearance of fresh MI, recent coronary occlusion found at necropsy, or both

Joint European Society of Cardiology/American College of Cardiology criteria

Criteria for acute, evolving, or recent MI—one of the following:

1. Typical rise and fall of biochemical markers of myocardial necrosis with at least one of the following:
    a. ischaemic symptoms
    b. Q waves
    c. ischaemic ECG changes
    d. coronary artery intervention
2. Pathological findings of an acute MI

Criteria for established MI—any of the following:

1. Development of new pathological Q waves on serial ECGs
2. Pathological findings of a healed or healing MI

Despite these guidelines, the detection of perioperative myocardial injury remains imprecise. Landesberg and colleagues reported that during 11,132 patient hours of ambulatory ECG monitoring after surgery, 38 of 185 consecutive patients had 66 transient ischaemic events, but only 12 patients (6.5%) sustained perioperative MIs [64]. Furthermore, Kirwin and coworkers were unable to correlate silent myocardial ischaemia on preoperative continuous ambulatory monitoring with perioperative MIs [65]. The use of symptomatology in the diagnosis of perioperative cardiac events is confounded by the fact that many symptoms are atypical or absent in as many as 75% of patients who have objective evidence of MI [60]. Traditional cardiac biomarkers such as creatine phosphokinase and its isoenzymes lack specificity for myocyte injury and are also released from skeletal muscle during surgical intervention or an ischaemia-reperfusion insult.

Cardiac troponins are calcium regulatory proteins of the thin actin filaments of the cardiac muscle [66]. Release of these proteins is now recognized to be a highly sensitive and specific marker of myocardial injury. Cardiac troponins are detected using monoclonal antibodies against several different epitopes of the troponin T or I molecule [66]. These antibodies, in particular Troponin I, have negligible cross reactivity with skeletal muscle [68]. Cardiac troponins start to rise within 3-4 hours after myocardial infarction and remain raised for 4-10 days because of a gradual degeneration of myofibrils with release of the troponin complex [69,70]. The joint committee of the European Society of Cardiology, the American College of Cardiology, and the American Heart Association have recently accepted their measurement in serum as the standard biomarker for the diagnosis of acute

myocardial infarction [63]. Similarly, Andrews and colleagues have demonstrated that Troponin I levels are accurate in the detection of myocardial ischaemia in patients undergoing vascular surgery [71].

In patients with acute coronary syndromes, elevation of cardiac troponins confers prognostic information in terms of cardiac morbidity and mortality. Patients with raised troponins have a risk of death that is several times greater than patients without elevated troponins [63,67]. Its use in immediate cardiac risk stratification is even advocated in the emergency setting. Interestingly, troponins have also been shown to predict overall mortality in patients whose primary pathology is non-cardiac in origin. This is true of populations as disparate as patients with sepsis, patients with renal failure and patients undergoing elective vascular and other non cardiac surgery [66].

Data for patients undergoing elective vascular surgery have shown that perioperative elevation of cardiac troponin, even at low cutoff levels, is an independent predictor of both short-term and long-term outcomes [72-74]. These include both perioperative myocardial infarction and subsequent all-cause mortality. Specific analysis in patients undergoing elective aortic surgery has shown that between 15-29% will have a perioperative elevation in serum troponin [75,76]. These elevations correlate with the occurrence of cardiac complications. The impact of emergency aortic surgery on troponin release is less well documented though preliminary data suggests that up to half of patients will suffer myocardial injury[76]. The impact of these findings on subsequent outcome is unknown.

1.8. Inflammation

As discussed earlier, inflammation is integral to the pathobiology of aortic aneurysms. Its local manifestation is highlighted by the inflammatory cell infiltration seen on histological examination of AAA tissue. However, the impact of inflammation, and in particular, a systemic inflammatory response seems to extend beyond this and influence outcome after aneurysm rupture.

Death and postoperative morbidity in patients who undergo technically successful repair of a ruptured aneurysm is generally attributed to the development of multiorgan failure [62]. This is due to an intense acute systemic inflammatory response caused by the failure to maintain control of the pro-inflammatory stimuli associated with emergency aneurysm repair [77]. The activation of inflammatory pathways is triggered by the obvious insults of massive haemorrhage, hypothermia and ischaemia-reperfusion. However, inflammatory pathways may already be primed in the build up to aortic rupture by the local inflammatory responses in the aortic wall that have already been described.

The acute phase proteins are a family of proteins that include C-reactive protein (CRP), fibrinogen and serum amyloid A. Their concentrations change in response to injurious stimuli and they are thought to facilitate the acute inflammatory response [78]. C-reactive protein was described almost 70-years ago as a serum protein that bonded to the C-polysaccharide of *Streptococcus pneumoniae*. It is produced primarily by hepatocytes, and to a lesser degree arterial smooth muscle cells, under the induction

of proinflammatory cytokines such as interleukin-6 and tumour necrosis factor-α [79]. Since then, it has become established in clinical practice as a non-specific, biomarker of systemic inflammation and the acute phase response.

As the association between inflammation and vascular disease (atherosclerotic and aneurysmal) is increasingly accepted, it may be extrapolated that biomarkers of inflammation will be elevated amongst patients with aneurysmal disease [80-83]. Elevated baseline levels of CRP may reflect low-grade vascular inflammation as a consequence of underlying aneurysmal change. These proteins may, potentially, represent a marker of inherent rupture risk.

Preliminary evidence exists to support such a hypothesis. Powell and colleagues have shown that CRP is elevated among patients with AAA while Engstrom and co-workers have shown that patients who go on to develop aneurysmal disease have raised serum inflammatory markers [84,85]. Recently, it has been shown, from retrospective data, that inflammatory markers, such as CRP and leucocyte count, are elevated in patients with acutely symptomatic AAA [86]. These findings have not been reported in patients with asymptomatic aneurysms.

Data from patients with pancreatic, renal and colonic cancers have shown that raised CRP levels confer prognostic information in terms of disease survival [87]. Similar findings are also seen in patients with critical illness [88]. It is unclear whether raised inflammatory biomarkers in patients with ruptured AAA can also be related to outcome and survival.

1.9. Natural history studies

There are few true natural history studies in patients with AAA; where the outcomes for patients with treated AAA and those with untreated AAA are randomised and compared prospectively.

Contrary to popular belief, the natural history of non-operated AAA is not one of uniform progression to aneurysm rupture. Much available natural history data stems from the subgroup of patients with large AAA who have been turned down for elective repair. Szilagyi and colleagues reported on 156 patients with AAA but unfit for surgery [89]. Two-thirds of these AAA were <6cm in diameter. More than half of their patient group died of a cardiovascular or cerebrovascular cause rather than an aneurysm related death and 5-year survival was 17 percent.

More recently, Lederle and colleagues have reported on a multicentre study of 198 patients with AAA >5.5cm for whom elective repair was not planned due to medical comorbidity or patient refusal [90]. The one-year rupture risk for AAA of 5.5 to 5.9cm was 9.4 percent, 10.2 percent for AAA of 6.0 to 6.9cm and 32.5 percent for AAA of >7cm. Interestingly, the risk of rupture in the smallest AAA diameter cohorts was significantly greater than that reported in randomised controlled trials. This finding has been reported across other studies and it is likely that patients with significant coexistent morbidity are at a higher risk of rupture than their healthier counterparts. Previous work from our group has also shown that patients with AAA > 5.5cm, but unsuitable for operative repair, were more likely to die of a non-aneurysm related cause [91].

So what of the rupture risk in patients with AAA fit for operation? Data on rupture risk are less readily available and susceptible to significant selection bias. Pooled data would suggest that AAA of 5.0-5.9cm, 6.0-6.9cm 7.0-7.9cm and >8cm have an annual rupture rate of 3-15 percent, 10-20 percent, 20-40 percent and 30-50 percent respectively [92-94]. It is acknowledged that not all AAAs rupture at a specific diameter and that other patient and aneurysm specific variables influence rupture risk. Variables, apart from aneurysm diameter, that have been reported to increase risk are female sex, hypertension, chronic obstructive pulmonary disease (COPD), cigarette smoking, familial history of AAA and saccular or eccentric aneurysms [92,95,96].

1.10. Outcome of ruptured AAA

As already described, the incidence of AAA and emergency AAA related hospital admissions have steadily increased over the past 20-years. Consequently, the crude mortality rates for aneurysm related deaths have also increased. These developments have taken place during a time in which there have been significant improvements in perioperative care and anaesthesia. It is intuitive to expect these factors to have had a positive impact on outcomes after ruptured AAA. In general, a contemporary operative mortality rate of 40% continues to be quoted for ruptured AAA repair [1]. However, there are conflicting data within the literature and mortality rates varying from 21% to 94% are reported [97,98]. Twenty-five years ago, Fielding and colleagues reported on 174 patients with ruptured aneurysms operated on between 1960 and 1978. In this historical series, operative mortality was 42% [99]. Why should there be such variability in reported mortality data and have outcomes over the past three decades genuinely failed to improve significantly?

Variation in reported mortality rates after AAA surgery are not confined to emergency repair alone. Similar discrepancies are seen in the reporting of results after elective aortic surgery too [100]. This has been blamed on the different types of study design used, i.e. prospective versus retrospective and hospital-based versus population-based. Blankensteijn and colleagues have proposed a methodology for the classification of evidence as illustrated in Table 1.10.1 [100].

Table 1.10.1. Blankensteijn's modified classification of levels of evidence.

Level of evidence	**Definition**
Level 1a	Prospective population-based studies
Level 1b	Prospective hospital-based studies
Level 2a	Retrospective population-based studies
Level 2b	Retrospective hospital-based studies
Level 2c	Retrospective hospital-based studies concerning selected groups

In their review of mortality after elective AAA repair, they concluded that there was a consistent disagreement in mortality rates between hospital based and population based studies. Nevertheless, prospective population based studies are recommended for their inclusion of large sample sizes with narrow confidence intervals, and prospective hospital based studies permit more detailed, accurate observations. The weaknesses of level 2 studies are numerous and relate to the inevitable biases associated with retrospective observational studies. These findings are clearly not restricted to elective AAA repair and are likely to be even more heightened in the context of emergency aneurysm surgery.

In determining contemporary mortality figures for ruptured AAA repair, the recent meta-analysis by Bown and colleagues provided useful data [1]. These authors reviewed all English language publications reporting on operative mortality after ruptured AAA repair from 1966 to 1998. They were able to identify 171 articles that met their selection criteria. Of these, 12 were prospective studies. However, careful analysis revealed that four of these studies were in fact retrospective analyses. Extension of their search of the literature up to 1st January 2005 identified a further 16 studies reporting on ruptured aneurysm operative mortality, of which only two were prospective. Thus, over a period of almost 40-years, there have been only 10 prospective English language studies published describing mortality after ruptured AAA repair (Table 1.10.2) [101-110]. The total number of patients studied in these series was 879 patients and the median (range) operative mortality rate from these ten studies was 42 (22-60) %.

Table 1.10.2. Ten prospective studies reporting operative mortality after ruptured AAA repair

Author	Year of Publication	Number of patients	Deaths (%)
Boyle [101]	2003	79	26 (33)
Hsiang [102]	2001	134	71 (53)
Magee [103]	1997	35	13 (37)
Koskas & Keiffer [104]	1997	158	73 (46)
Lazarides [105]	1997	40	22 (55)
Passke [106]	1994	36	8 (22)
Johnston [107]	1994	147	73 (50)
Scott [108]	1992	63	19 (30)
Collin [109]	1989	75	27 (36)
Amundsen [110]	1987	103	62 (60)

Bown's analysis reports an overall published operative mortality of 48%. Meta-regression analysis over the study period demonstrated a gentle decline in mortality with time. Mortality in 1960 was in the region of 55%, for 1980 it was 48% and for 2000 it is 41% [1]. The average operative mortality reported in the ten prospective studies from 1966 to 2005 of 42% was in keeping with this figure. The authors do point out the striking heterogeneity in the results. Mortality ranged from 0 – 94%, though these outlying results generally stemmed from small sample sizes.

Bown and colleagues cautioned against potential biases that may have influenced their meta-analysis. In particular, they were able to detect considerable bias in the reporting of intraoperative mortality from single centre reports. This together with publication bias against, what may be perceived, as bad results due to poor surgical performance are likely to down play true mortality rates. It is interesting to note that of the 10 prospective studies available, those with the lowest mortality rates are from one or two collaborative centres, while those series with the highest mortality are true multicentre data.

In summary, operative mortality after ruptured AAA remains prohibitively high. Although there appears to have been a slight improvement in outcome over the past 40-years, operative mortality continues to lie in the region of 40-50%.

1.11. Predicting mortality after ruptured AAA

Most surgeons practice a selective policy of operative intervention for patients with ruptured AAA[2]. This approach is underpinned by the rapid assessment of the patient's clinical condition on presentation and premorbid health and functional status to determine if attempted operation is appropriate, and associated with a realistic chance of survival. It aims to ensure healthcare resources are utilised appropriately and avoid futile attempts at intervention in patients with prohibitive risk. In clinical practice, this patient selection is largely based upon subjective criteria. However, to ensure that selection is objective, a system that can accurately predict outcome in patients with ruptured AAA is crucial.

Many authors have attempted to identify variables capable of predicting mortality in patients with ruptured AAA. There is much heterogeneity in the nature and quality of results and the methods used for reporting. A few series have gone further, and have performed statistical modelling on predictive variables to design scoring systems that can forecast outcome. However, many systems have not utilised sound methodology in their design. Furthermore, only the minority have undergone robust audit, let alone prospective validation. A previous review has recognised that these limitations would render meta-analytical techniques unsuitable[1]. The following systematic review considers existing scoring systems and existing literature on variables predictive of outcome in patients with ruptured AAA.

1.11.1. Hardman Index

The Hardman scoring system is, probably, the best known of the available scoring systems for use in patients with ruptured AAA. Originally described in 1996, this retrospective series reviewed 154 non-consecutive patients who underwent operation for ruptured aneurysm between 1985 and 1993 at a single Australian tertiary vascular centre[111]. Sixty-seven preoperative variables on 136 patients were subjected to univariate analysis for their association with death in hospital, or within 30-days of surgery. Continuous variables significantly associated with mortality were categorized into quartiles, and the mortality of each category examined. All variables related to postoperative death were further analysed alongside data from another 18 patients to develop a multivariate model. The significant multivariate risk factors were then assessed for their cumulative effect when weighted equally.

Five independent variables were identified on multivariate analysis: preoperative haemoglobin of less than 9g/l, serum creatinine of more than 190umol/l, electrocardiographic evidence of myocardial ischaemia, in-hospital loss of consciousness and age greater than 76 years. No single risk factor had a predictive value in isolation, but the cumulative predictive value of the risk factors is shown in Table 1.11.1. Although each variable was given equal weighting, odds ratios ranged from 2.90-6.63. The presence of three or more of the five risk factors was associated with a 100% mortality rate Table 1.11.2.

Table 1.11.1. Multivariate model of Hardman Index variables independently associated with mortality

Variable	P value	Odds ratio	95% CI
Age >76 years	0.001	4.69	1.93-11.5
ECG ischemia	0.004	6.63	1.81-24.3
Cr >190 umol/L	0.005	4.07	1.54-10.8
Loss of consciousness	0.020	5.37	1.30-22.2
Hb <9 g/l	0.032	2.90	1.10-7.71

Table 1.11.2. Mortality of patients with multivariate model of five equally weighted Hardman Index variables according to number of variables present

No. of variables present	No.	Deaths	Percent
0	62	10	16%
1	52	19	37%
2	32	23	72%
3 or more	8	8	100%

Following its conception, the Hardman score was commended for its simplicity and practicality in the acute setting. Validation of the system has been performed at various levels. To date, there have been five studies that have assessed the performance of the Hardman system [101,111-4]. These are illustrated in Table 1.11.3.

Figure 1.11.1 CT image of ruptured AAA

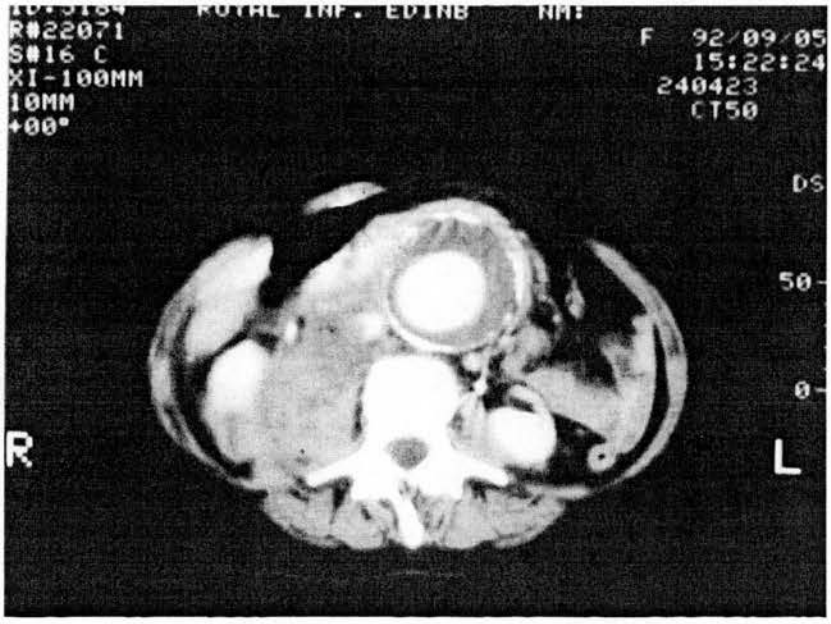


Table 1.11.3. Operative mortality (%) in five series examining the presence of Hardman variables in patients with ruptured AAA and relationship with death.

	Hardman Variables			
Series	0	1	2	≥3
Hardman et al. 111	16%	37%	72%	100%
154 patients				
Prance et al. 112	18%	28%	48%	100%
69 patients				
Neary et al. 113	35%	55%	74%	90%
188 patients				
Boyle et al. 101	8%	24%	55%	100%
79 patients				
Calderwood 114	40%	46%	77%	92% *
137 patients				

* Mortality for 3 risk factors only. For 4 risk factors, mortality was 100%

On initial inspection, these results seem to support the original data of Hardman and colleagues. Of the five series, 3 or more positive variables are uniformly associated with perioperative death in three studies. However, it is disconcerting that two of the reports contain patients with 3 or more variables who survived operative repair. Although it has been widely concluded that the presence of more than 3 Hardman variables is a good predictor of death, it would seem that this is not universally true. More critical analysis of these data reveals that all but one review is retrospective in nature and the only prospective data are compiled from two centres[101]. These data do add some credibility to the validity of the Hardman scoring system, they do highlight that the instrument is not as sensitive as initially reported and do emphasise the need for further prospective validation before its use in clinical practice can be supported unanimously.

1.11.2 Glasgow Aneurysm Score

The Glasgow Aneurysm Score (GAS) was first reported in 1994[115]. This instrument was originally developed as a tool for prognostic scoring in patients undergoing repair of either intact or ruptured AAA. A retrospective, multi centred, non-consecutive sample of 500 patients undergoing aneurysm repair at general surgical units in Glasgow between 1980 and 1990 was examined for risk factors associated with death. Using multivariate analysis, the following independent risk factors were identified: age ($P = 0.02$), shock ($P = < 0.001$), myocardial disease ($P = 0.02$), cerebrovascular disease ($P = 0.02$) and renal disease ($P = 0.003$). Myocardial disease is typified by documented myocardial infarction and/or on-going angina. Cerebrovascular disease refers to all grade of stroke including transient ischaemic

attacks. Renal disease is a history of chronic or acute renal failure and/or urea greater than 20mmol/l and/or creatinine over 150μmol/l at presentation. Rounding of the regression coefficients created a simple risk score: risk score = (age in years)+(17 for shock)+(7 for myocardial disease)+(10 for cerebrovascular disease)+(14 for renal disease). Appraisal of the scoring system showed that mortality rate increased in proportion to score. The same authors went on to evaluate prospectively their system in a subsequent multicentered study[116]. Again, they reported similar results to the original analysis used in developing the score. Mortality was found to correlate well with GAS and scores of >95 were related to a mortality rate of >80%.

There has been little further validation of this generic scoring system for patients undergoing repair of an aortic aneurysm. Given its simplicity, ease of use and apparent predictive power, this seems surprising. However, recently, a Finnish group have examined the performance of the GAS in a retrospective review of 836 patients with ruptured AAA admitted to 21 hospitals and included in a large national vascular registry[117]. These data were able to confirm that GAS was independently associated with postoperative death. In this series there was no cut-off score that predicted a postoperative mortality rate of 100 %, though a score of >98 was associated with a mortality rate of approximately 80%. It would appear that the GAS is a useful tool in predicting outcome after AAA rupture but, again, further evaluation is needed.

1.11.3. POSSUM

The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) was described and prospectively validated by Copeland

and colleagues in 1991[118]. Its primary function was as a scoring system for general surgical audit, to allow for the effects of case-mix, rather than as an instrument to predict individual case outcome. It represents a risk-prediction model based on a physiology score derived from 12 preoperative variables, independently predictive of adverse postoperative outcome on multivariate analysis, and an operative score derived from six variables. Each of the variables is graded and scored exponentially as 1, 2, 4 or 8. The combined physiology and operative scores were subjected to logistic regression analysis to generate risk equations that convert the scores into a predicted percentage morbidity and mortality. However, attempted validation in both general and subspecialty surgery has reported a lack of calibration of the initial model and suggestions for remodelling of the regression equation have been proposed [119-122]. This led to the Vascular Surgical Society of Great Britain and Ireland developing a risk equation specific for vascular surgery (V-POSSUM) [123]. Furthermore, specific evaluation of the POSSUM system in ruptured AAA repair demonstrated that the equation performed poorly in emergency aortic surgery [105]. Subsequently, two further equations (one incorporating both physiology and operative scores, while the other only used the physiology score) specifically for ruptured AAA were derived from a retrospective series of 106 patients [124]. Initial validation was performed by the authors on a further set of 107 patients with ruptured AAA. The physiology only equation, though effective, was found to have a lack of fit at a certain risk range. However, the ruptured AAA POSSUM (RAAA-POSSUM) equation that combined physiology and operative scores was more successful at accurately predicting outcome. There have been two further series that have examined the validity of both RAAA-POSSUM systems. Retrospective data on

188 patients from Gloucester with ruptured AAA were subjected to both equations[113]. Interestingly, both systems performed well with no difference in observed and expected mortality results. A further non-consecutive, retrospective series of 68 patients who survived for more than 24h after repair of a ruptured AAA from Leicester also confirmed that although the two systems tended to slightly over-predict mortality, there was no statistically significant lack of fit [125]. However, the limitations of this highly selected data set are obvious.

To date, there has been no prospective validation of the RAAA-POSSUM systems. Alhough the existing evidence suggests that they perform well, the utility of the POSSUM system in clinical decision-making is questionable. It is important to reiterate that the POSSUM methodology is principally for comparative audit. The need for operative variables renders most POSSUM equations impractical for preoperative risk prediction. The data required for the physiology RAAA-POSSUM tool are easily recorded, though the need for complex mathematical equations can make its utility cumbersome in the clinical setting. The system allows for more precise risk stratification of patients than some of the other systems already described. This level of accuracy may introduce even more complexity to clinical decision-making. In the Gloucester study, one of 16 patients with a predicted mortality risk of more than 80% survived and three of 21 with a risk of 70-80% survived [113]. Using this system, the absolute prediction of operative futility would appear unfeasible.

1.11.4. Vancouver Scoring System

Of scoring systems applicable to patients with ruptured AAA, the Vancouver system is probably the least well known and utilised. Also reported in 1996, this retrospective series examined 147 patients who underwent repair of a ruptured aneurysm between 1984 and 1993 [126]. Perioperative demographic and physiological variables significantly associated with death on univariate analysis were subject to further multivariate analyis.

Univariate analysis identified age, reduced conscious level, preoperative cardiac arrest, history of myocardial infarction and a history of collapse as being associated with postoperative death. After multivariate logistic regression analysis, age, reduced conscious level and preoperative cardiac arrest remained as significant predictors of death Table 1.11.4.

Table 1.11.4. Vancouver scoring system predictive variables

Variable	**Category**	**Coefficient (Constant= -3.44)**	**Odds ratio (95% CI)**	**P value**
Consciousness	Conscious	-1.14	3.1 (2.2-4.4)	<0.01
	Unconscious	1.14		
Age		0.062 x age	1.9 (1.5-2.3)	<0.01
Cardiac arrest	Yes	0.60	1.8 (1.4-2.4)	0.03
	No	-0.60		

These variables could be entered into a predictive model equation on the basis of the coefficients from the logistic regression model. The probability of death is estimated using the equation $e^x / 1 + e^x$, where e is the base of the natural logarithm and x is the constant + sum of coefficients for the significant variables.

The Vancouver group have also attempted to validate their statistical model. They evaluated the performance of the instrument on a prospective series of 134 patients drawn from two tertiary centres [102]. The authors contend that their system is accurate at predicting patients at extreme risk (patients with a predicted mortality >90%). However, the instrument seems to perform less well at lower levels of mortality risk (patients with a predicted mortality >80%). The group concluded that their tool was of use in informing clinical decisions in patients with ruptured AAA, though unable to identify a 100% mortality rate. Despite their assertion, this scoring system does not seem to have gained support and been utilised by other centres. No further independent validation is identifiable in the literature. Reasons for this may be related to the cumbersome nature of the model. Though the variables utilised are easily obtained, the need for coefficients and complex mathematical formula renders it less practicable in the acute situation. The derivation of a percentage risk of death is similar to the GAS and POSSUM systems. It may be that this instrument has a utility for risk stratification for the purposes of audit, though more robust validation is needed to assess its credentials. Its use in clinical decision-making in the acute setting may be hampered by its complexity.

1.11.5. Other predictive variables

Interest in the prediction of clinical outcome in patients with AAA rupture is highlighted by the publication of more than 60 independent series investigating the subject in the last 20 years alone. Though the preceding scoring systems are, perhaps, the most sophisticated and well cited of these articles, the remainder also offer potentially useful data to inform clinical judgement.

Of these further articles, eight report negative results and were unable to identify any preoperative variables predictive of death after aneurysm rupture (Table 1.11.5) [125,127-33]. These studies, on 710 patients from European and North American centres, are all retrospective in design. The median (range) sample size and mortality was 92 (33-140) and 49% (32%-64%) respectively. These data provide compelling evidence for the argument that absolute prediction of outcome, in this disease, is impossible. It is argued that withholding an operation on the basis of any predictive variables is unsound and ethically unjustified [129]. Some of the most highly regarded authorities in vascular surgery have championed this thesis [134]. It may also be assumed that there is an even greater body of similar unpublished data in existence owing to the nature of publication bias.

Table 1.11.5. Series failing to identify variables predictive of death after operation.

Author	Year of publication	Number of patients	Deaths (%)
Campbell [127]	1986	52	56
Vohra [128]	1988	92	39
Harris [129]	1991	113	64
Meesters [130]	1994	99	49
Barry [131]	1997	140	52
Hatori [132]	2000	33	39
Bown [125]	2003	139*	32
Sultan [133]	2004	42	60

* Excludes patients who died within 24h of operation

However, examination of the available data generates some concerns. Of the three series that study more than 100 patients, one excluded patients who died within the first 24h of operation and another shared a dataset with a further publication, that a year later reported female gender, preoperative hypotension, low haemoglobin and thrombocytopenia as being predictors of mortality [125, 131]. Critics also have questioned whether 'cardiac arrest' in these series simply represented an inability to palpate pulses due to hypotension or arrhythmia rather than true cardiac asytole. Nevertheless, irrespective of these deficiencies, such data cannot be ignored.

The remaining 54 series all describe one or more preoperative variables that were predictive of outcome in 80944 patients (Table 1.11.6). The median (range) number of patients studied was 119 (18-67751) and median (range) mortality was 47% (13%-75%). It is noteworthy that only two studies were prospective in design [104,107]. Most data have been subjected to multivariate statistical tests, where appropriate, though some large series have only undertaken univariate analysis. Apart from Hardman, no other group has robustly identified preoperative variables, either individually or in combination, that are capable of defining a group with such a prohibitive risk of death as to preclude intervention. Even patients with preoperative cardiac arrest, a subgroup, intuitively, at extreme-risk of mortality, are reported to have survival rates of up to 33% in certain series [158].

Nevertheless, 10 variables regularly appear as significant predictors of death. If one takes haematocrit and serum haemoglobin as analogous variables, six of these appear more frequently than others. These six include hypotension, advanced age, cardiac

arrest, raised serum creatinine, low haemoglobin/haematocrit and a history of ischaemic heart disease. These variables or their correlates are all represented in the established scoring systems described earlier. Though the risk factors of hypotension, cardiac arrest, raised creatinine, low haemoglobin, loss of consiousness and ECG ischaemia have retained independent statistical significance on multivariate analysis; they are all implicated in the development, or a manifestation of systemic shock. Furthermore, more than half of these 54 publications identified hypotension as a predictor of mortality. Of the reported risk factors, female gender is, perhaps, the most difficult to interpret. Four of the five datasets that describe this finding are North American and have considerable sample sizes. The overrepresentation of women in elective and emergency AAA mortality statistics is well described though reasoning remains uncertain [180].

The existing literature suggests that there are preoperative variables associated with perioperative death after AAA rupture. However, there is much to be desired in terms of the quality and level of available evidence. In the past 20 years, there have been no more than two published, prospective attempts to investigate risk factors associated with death after aneurysm rupture. At present, no scoring system, or variables, in combination or on its own, can be persuasively recommended as being predictive of perioperative death and be utilised to influence treatment decisions. Of the scoring systems in existence, none have been adequately validated to be of use in dictating therapy or justifying clinical decision-making. At best, they are useful to risk stratify patients for the purposes of audit and act as an adjunct to supplement

clinical intuition. Until a scoring system that utilises sound methodology and robust validation is available, experienced clinical judgement will remain of foremost importance in the selection of patients for ruptured AAA repair.

Figure1.11.2. Perioperative photo of completed open repair of AAA

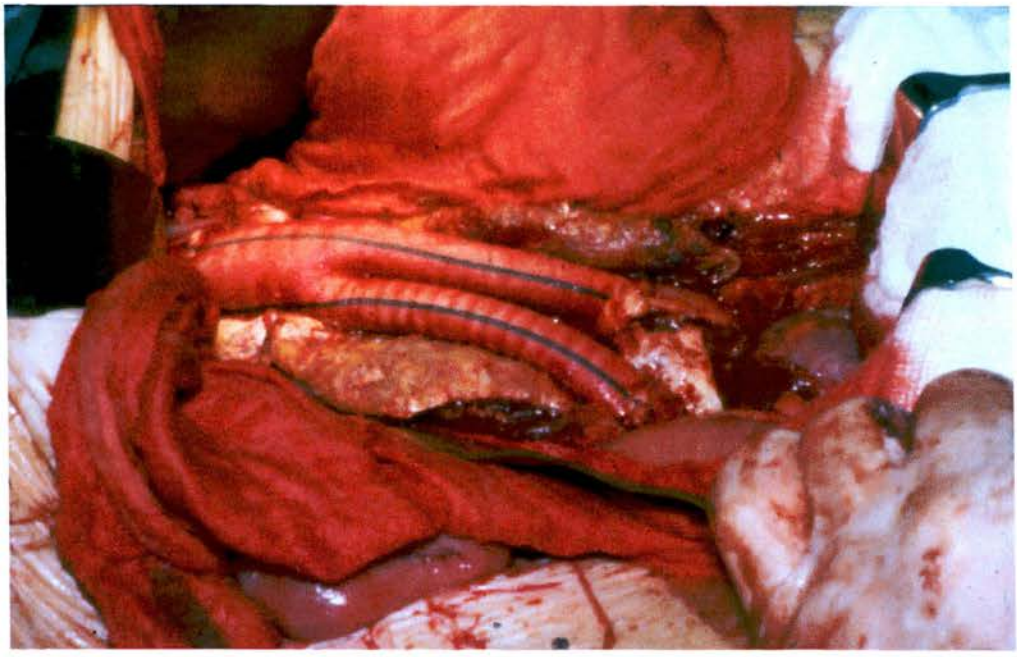


Table 1.11.6. Series identifying preoperative variables predictive for death after attempted repair of ruptured AAA.

Author	Year of publication	No. of patients	Deaths (%)	BP (mmHg)	Age (Yrs)	Cardiac arrest	Creatinine (μmol/l)	Hb (g/l)	Hct (%)	IHD	LOC	Sex (M/F)	ECG changes	Platelets ($x10^9$/l)	Other
Donaldson *et al.*[135]	1985	81	43		• (>76)*				• (<30)*				•*		
Lambert *et al.*[136]	1986	180	75	• (<80)						•					Hypertension
Morishita *et al.*[137]	1986	20	45	•*											Duration of symptoms*, associated disease*, duration of AAA
Nachbur *et al.*[138]	1987	116	47		•*										Duration of symptoms <6h*
Shackleton *et al.*[139]	1987	106	40								•				Cardiac failure, Anion gap
Martin *et al.*[140]	1988	58	26	• (<90)											
Amundsen *et al.*[110]	1989	103	59	• (<92)	• (>71)										
Ouriel *et al.*[141]	1990	243	55	• (<70)			• (>300)								
Murphy *et al.*[142]	1990	172	49	• (<90)*		•*									Collapse*
Johansen *et al.*[145]	1991	186	70		• (>80)*	•*						• (F)*			
AbuRahma *et al.*[144]	1991	73	62	• (<90)											Collapse
Gloviczki *et al.*[145]	1992	231	42	•					•						APACHEII score
Rosenthal *et al.*[146]	1992	47	43	• (<90)*	• (>75)*	•*									Treatment delay*
Scott *et al.*[108]	1992	66	30		•‡										

Bauer *et al.*[147]	1993	314	29	• (<90)						•					
McCready *et al.*[148]	1993	208	50	• (<90)	• (>70)										
Katz *et al.*[149]	1994	99	57		•				•						
Johnston *et al.*[107]	1994 †	147	49				• (>130)								
Katz *et al.*[150]	1994	1829	50	•								• (F)			Chronic renal failure
Panneton *et al.*[151]	1995	112	49	• (<90)		•									
Browning *et al.*[152]	1995	54	44	• (<85)						•					
Marty-Ane *et al.*[153]	1995	61	13		•										
Farooq *et al.*[154]	1996	122	56	• (<80)		•									
Jaakkola *et al.*[155]	1996	48	65	• (<90)						•					
Rutledge *et al.*[156]	1996	1480	54		• *							• (F)*			
Chen *et al.*[126]	1996	157	46		•	•					•				
Hardman *et al.*[111]	1996	154	39		• (>76)		• (>190)	• (<9)			•		•		
Koskas *et al.*[104]	1997 †	158	47	•	•		•								Stroke / Transient Ischaemic Attack
Martinez *et al.*[157]	1997	84	57	• (<90)	•										
Lazarides *et al.*[105]	1997	40	55											•	
Halpern *et al.*[158]	1997	96	60	• <90			• (>150)	• (<10)			•				

Satta *et al.*[159]	1997	51	47	•*				•*							
Subramaniam *et al.*[160]	1998	18 *	67	•*				• (<10)*							Chronic Obstructive Pulmonary Disease *
Barry *et al.*[161]	1998	150	48	•*				•*				• (F)*		•*	
Dardik *et al.*[162]	1998	527	47		•					•					Chronic Obstructive Pulmonary Disease
Van Dongen *et al.*[163]	1998	309	25		• (>70)										
Sasaki *et al.*[164]	1998	27	22	• (<80)	•										
Urwin *et al.*[165]	1999	135 *	63		•	•									
Ho *et al.*[166]	1999	40	48		•										
Kniemeyer *et al.*[167]	2000	57	32	• (<80)				• (<9)					•	• (<100)	
Turton *et al.*[168]	2000	102	53	• (≤90)		•									
Heller *et al.*[169]	2000	67751	46		• (>70)		•					• (F)			Afrocaribbean race
Lovricevic *et al.*[170]	2000	54	30	•‡		•‡					•‡				
Merlo *et al.*[171]	2001	123	45		•*									• (<100)*	Hypertension*
Noel *et al.*[172]	2001	413	37			•			•						APACHE II
Alonso-Perez *et al.*[173]	2001	144	47	• (<80)	•										
Gutierrez – Morlote *et al.*[174]	2002	106	49	• (<90)									•		
Hans *et al.*[175]	2003	101	48		•				• (<35)						Treatment delay

Piper *et al.*[176]	2003	147	35												Core temp
Markovic *et al.*[177]	2004	229	54	• (<95)*		•*	• (>180)*	• (<10)*	• (<29)*	• *	•*				Low urine output*, Leucocytes > $14x10^9$ $x10^9$/l *, Urea >11mmol/l*
Lo *et al.*[178]	2004	41	41				•								
Dueck *et al.*[179]	2004	2601	41		•							• (F)			
Calderwood *et al.* [114]	2004	137	56	• (<100)	• (>76)		• (>190)						•		
Korhonen *et al* [117]	2004	836	47	•											

LOC Loss of Consciousness
BP Blood Pressure
Hb Haemoglobin
Hct Haematocrit
IHD Ischaemic Heart Disease

† Prospective studies
* Univariate analysis

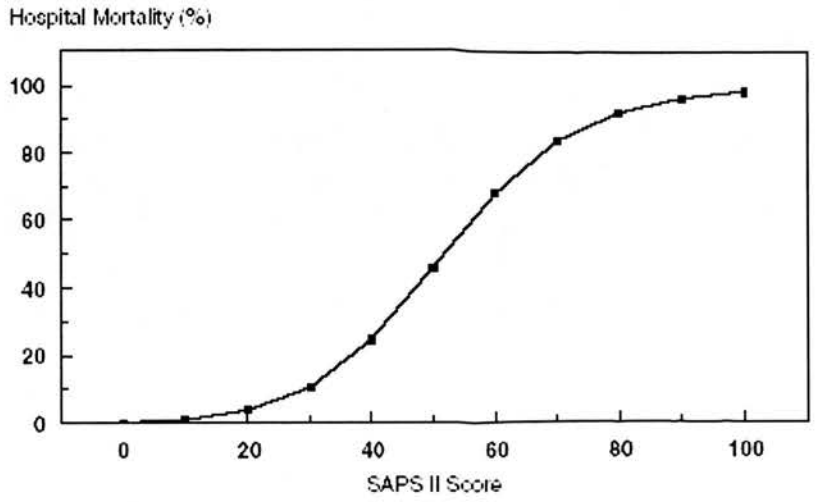
1.12. Scoring systems

A risk scoring system aims to consider a patient's characteristics and generate a treatment independent risk of death. It attempts to rationalise and quantify a number of patient related variables into a single number whose value corresponds to the severity of the condition. Independent variables are selected using statistical modelling techniques of which multiple logistic regression is the most common. The use of scoring systems extends from comparative audit and research to clinical decision-making. If a scoring system is to be put into clinical practice, it is essential that it has undergone appropriate and robust validation. Furthermore, scoring systems can evolve with time as further analysis and remodelling can improve their predictive power.

The prediction of outcome for a given patient is subtly distinct from illness severity scoring. Scoring systems aim to describe outcome as a statistical probability, ranging from 0 to 1, that is derived from a measure of illness severity[181]. Therefore, it is almost impossible for scoring systems to make absolute predictions of outcome. Rather, it is possible to make predictions based on the assumption that that there is an acceptable level of uncertainty. Thereby, if a 95% threshold of uncertainty is chosen, it is assumed that probabilities equal or greater than 0.95 are associated with certain prediction. It is rare for a scoring system to achieve such a high level of sensitivity that major decisions on treatment withdrawal and limitation can be made safely. Furthermore, there are certain intrinsic mathematical weaknesses with the development of risk scoring systems. These flaws undermine, to an extent, the reliability and predictive value of existing systems.

Multiple logistic regression techniques are the most common statistical tool used in the development of outcome prediction models. However, this technique is based upon two assumptions that are not strictly fulfilled in outcome prediction. In a regression analysis, it is best for the outcome variable to be continuous. Clearly, in outcome prediction the variables are death or survival and are categoric in nature. Secondly, an assumption is made that there is a linear relationship between the dependent and independent variables. Again, it is unusual for mortality to display such a linear association and a sigmoid relationship is more typical. This is illustrated in Figure 1.12.1.

Figure 1.12.1. The sigmoid shaped curve of risk of hospital mortality against the Simplified Acute Physiology Score II [182]



Selection bias in the recruitment of patients to the original dataset, upon which a scoring system is derived, can impair performance. Bias may also arise as a result of small sample size or inadequate case-mix. This may be the case if a dataset is limited to a single centre. In such cases, further validation in independent institutions is necessary. It is also acknowledged that generic scoring systems underperform when utilised in specific patient subgroups i.e. burns patients, paediatric patients. As a result disease-specific scoring systems are preferable where possible. However, in conditions with a low prevalence, it may be difficult to acquire a satisfactory sample dataset on which to develop a scoring system.

The outcome measures that are used most frequently are in-hospital or 30-day mortality. However, to a patient, their functional status on discharge is of great important. Nonetheless, this outcome measure and its prediction is largely neglected. In severe illness, the variables that may influence these outcomes are not confined to those that are at play at the point of initial presentation and assessment. Unfortunately, it is usually these initial variables that are utilised to score illness and predict outcome. Sequential scoring may circumvent this problem but may result in large amounts of conflicting data of little prognostic value.

Predictors for scoring system are generally selected from a combination of demographic, physiological and therapeutic variables. It is ideal to try and generate the most accurate value of risk scoring from the least number of predictors by excluding variables that do not influence outcome. The selection of these variables is performed by a combination of statistical modelling and on the basis of expert

opinion. However, even the selection of variables for statistical assessment itself introduces a subjective influence. Subjective judgement is also essential to select predictors that can be easily measured and are practicable.

Statistical selection is performed using backwards elimination and forward selection. An F statistic is generated to measure the contribution of variables to outcome. Variables with little influence are discarded. Forward selection then adds the variables with the strongest correlation coefficients until the most recently added variable falls below a critical value. The weakness of these techniques is their inability to assess indirect influences and variables with small effects. As a consequence, predictive variables may be excluded and contribute to the weakness of the instrument in making absolute judgements on outcome [183].

There are certain universal deficiencies common to the application of all scoring systems. As already described, selection bias may be introduced from the sample population that is used to derive a scoring system. Further bias may arise from the method of recording variables, and in variation in reporting clinical signs or symptoms. The desirable features in the application of a scoring system are data that can be easily accessed and recorded, but can also be collected consistently and accurately. This accuracy relates to any inter or intra observer variability. This has been highlighted by reports demonstrating a higher severity illness scores when automated information systems were used as opposed to manual recording [184]. Similarly, missing data may cause detection bias, and misclassification may occur when rapid patient assessment is needed.

With time, updating and modification of scoring systems may occur. Furthermore, systems may be adapted to suit specific patient subgroups or populations. The performance of a scoring system works best when it is customised to the behaviour of a local environment and population. This limits the applicability of the system across centres and hampers comparative audit. It also makes external validation difficult. Nevertheless, even with customisation, it is difficult for a scoring system to allow absolute predictions of outcome for an individual patient [185].

Any scoring system requires formal validation to assess its performance. Validation may be described in four stages. Firstly, the performance is assessed in the original development dataset. The instrument's performance is then assessed on a new but separate dataset from the same institution. If performance is maintained, the model can be applied to data from a separate centre. The instrument can then be compared against other predictive tools that are regarded as the 'gold standard' to determine if its performance is superior and it represents an advance [181]. Finally, the scoring system must have a useful clinical application.

Medical futility is regarded as having four independent aspects [186]. The first is physiological and involves a condition that is refractory to therapy. The second is imminent demise where, despite support, the patient's physiological stability cannot be restored and the patient succumbs. The third is a patient with a uniformly lethal condition (i.e. metastatic cancer) and the fourth where a patient's perception of their quality of life after therapy is deemed unacceptable and potential benefit is

outweighed by risk. It is the first and second that are most relevant in the patient with a ruptured aneurysm. This may be illustrated in the scenario of a patient who despite resuscitative measures and urgent surgical repair does not regain physiological stability and progressively deteriorates. A scoring system that could accurately aid in the identification of such patients would be a useful prognostic tool and adjunct to clinical judgement.

1.13. Quality of life

The traditional measures of surgical outcome have been in terms of perioperative morbidity and mortality. However, the importance of health-related quality of life (HRQoL) in the assessment of outcome has gained increased recognition. The rationalisation of health care finances has motivated the need to quantify outcomes of medical interventions and in the evaluation of cost, quality of life issues must be considered. Evaluation of a clinical intervention must not only take into account the traditional primary outcomes of death, disability or cure but also the patient's perspective of outcome. To assess the benefit of an intervention, evidence for the impact on the patient in terms of health status and HRQoL is essential [187].

The efficacy and durability of elective AAA repair in terms of perioperative morbidity and mortality, long-term survival, quality of life and cost-effectiveness are well-established [188-190]. The increase in the number of elective AAA repairs performed has not resulted in an associated decline in the incidence of ruptured AAA [191]. Despite advances in perioperative care, repair of ruptured AAA continues to be associated with an operative mortality rate of 45% and high attendant financial cost and resource utilisation [1,192]. Though survivors are reported to attain the same rates of survival as the normal population, functional outcome in terms of HRQoL is uncertain [193].

Clearly, it is impossible to assess HRQoL before RAAA surgery. However, prospective follow-up of survival and functional recovery is entirely feasible. Computerized and manual searches of the literature identified 14 studies

investigating quality of life in patients who had survived operative repair of ruptured AAA [194-206] (Table 1.13.1). Three articles from the original searches may be excluded from review, as they do not undertake objective HRQoL assessment [204-206]. All are retrospective-observational studies in design. The limitations of retrospective study are well established.

Of the 11 remaining studies, the time point between operation and HRQoL assessment ranged between nine and 156-months. Functional recovery displays a close temporal association and analogous studies of recovery following elective repair of AAA have shown that HRQoL returns to preoperative levels or better six-months after surgery [2]. The considerable variation in follow-up period between studies renders direct comparison difficult. With the progress of time following ruptured AAA repair, patients become increasingly selected in that they have survived to reach hospital, survived operative repair, survived their postoperative recovery and agreed to HRQoL assessment. It may be argued that this process specifically selects patients who are biologically more robust and predisposed to achieve good functional outcomes.

Of the 11 studies reviewed, 10 report good functional outcomes for survivors of ruptured AAA. Three of these 10 utilised HRQoL instruments designed by the authors and though they provide interesting data, the usefulness and sensitivity in determining functional outcome must be questioned.

Table 1.13.1. Studies quoting quality of life after ruptured abdominal aortic aneurysm repair in chronological order according to year of publication.

Reference	Year of publication	Study design	Age range (years)	Number of patients	HRQoL Instrument	Follow-up period (months)	Control group	Results
O'Donnell *et al.*[194]	1976	Retrospective	≥80	5	Authors design	unknown	▪ Elective AAA repair ▪ Non-operatively treated AAA ▪ Expanding AAA	Regained or improved physical status
Treiman *et al.*[195]	1982	Retrospective	≥80	7	Authors design	48-156	▪ None	Regained physical status at six-months
Rohrer *et al.*[193]	1988	Retrospective	59-84	26	Adapted from Self evaluation of life function scale	unknown	▪ Elective AAA repair	No difference in physical independence, psychological well-being social interaction. Reduced sense of general well being after RAAA
Van Ramshorst *et al.*[196]	1990	Retrospective	Unknown	55	Adapted from Self evaluation of life function scale & Psychosocial Adjustment to Illness scale	20-57	▪ Age and sex-matched elective AAA repair	No difference apart from reduced level of social behaviour
Magee *et al.*[197]	1992	Retrospective	Unknown	45	York QoL Questionairre & Rosser index	18-42	▪ Elective AAA repair	Deterioration in HRQoL
Currie *et al.*[198]	1992	Retrospective	≥80	9*	Authors design	unknown	▪ Elective AAA repair ▪ Age and sex-matched normal population	No differences
Gefke *et al.*[204]	1994	Retrospective	Unknown	41*	Authors design	unknown	▪ None	Unknown
Moriyama *et al.*[206]	1994	Retrospective	71†	32	Unknown	5-101	▪ Elective AAA repair	Unknown
Matsushita *et al.*[205]	1997	Retrospective	Unknown	≤17	Authors design	49†	▪ Elective AAA repair	Unknown
Hennessy *et al.*[200]	1998	Retrospective	54-81	14	Hopkins Symptom Checklist, General Health Questionnaire & Rosser index	4-29	▪ Age and sex-matched elective AAA repair	No differences
Eskandari *et al.*[199]	1998	Retrospective	70†	15	SF - 36	9-48	▪ Age-matched normal population	No differences
Bohmer *et al.*[201]	1999	Retrospective	54-85	28*	SF- 36	12-156	▪ Age-matched normal population	No differences
Joseph *et al.*[202]	2002	Retrospective	60-81	26	SF - 36	unknown	▪ Age-matched normal population	No difference / better HRQoL
Korhonen *et al.*[203]	2003	Retrospective	47-96	82	RAND-36	10-69	▪ Age & sex-matched normal population	No difference apart from reduced physical function

Of the seven studies that used validated HRQoL instruments and failed to establish a difference in HRQoL after ruptured AAA repair, one used the Hopkins Symptom Checklist and General Health Questionnaire, two were based on the Self-evaluation of life scale instrument and four utilised the SF36 or RAND 36. All four tools are generic instruments for HRQoL assessment and have been extensively used in theassessment of functional outcome. In particular, the reliability, validity, acceptability and consistency of the SF36, and its derivative the RAND 36, have been confirmed. The SF36 is the most widely used quality of life instrument in the medical literature and its use, as a quality of life measure in the assessment of vascular disease, has been previously recommended [207].

Though generic instruments are designed to be used for all kinds of disease, generic health questionnaires are disadvantaged in that they tend to lack sensitivity. Disease specific instruments are designed to assess HRQoL in specific patient populations assessing domains directly related to the impairments caused by the disease process [208]. Disease specific instruments are thereby likely to be more sensitive to changes between patients. However, to date no disease specific HRQoL instrument exists for use in AAA and functional outcome remains largely assessed using generic tools.

Only one study reported significantly reduced HRQoL in survivors of ruptured AAA. Magee and colleagues demonstrated a significant deterioration in functional outcome following ruptured AAA repair when compared to elective repair [197]. They noted a fall in HRQoL from near perfect health preoperatively to considerable disability at postoperative follow-up. Such a conclusive finding has not been reproduced in any

other series reporting on ruptured AAA survivors. However, previous prospective studies in patients surviving intensive care have shown similar reductions in HRQoL [209,210]. If such a finding were true for survivors of ruptured AAA repair, arguments for aneurysm screening and elective repair would be further supported.

In the United Kingdom, the financial cost of ruptured AAA repair has been reported to be almost double that of elective repair with an average cost of approximately £8000 [211]. Nevertheless, cost-analyses of surgical repair of ruptured AAA have shown that surgical treatment remains a cost-effective intervention [212]. The attainment of normal life expectancy after successful repair of ruptured AAA versus the alternative of immediate death is the predominant reason for such a finding. However, these analyses fail to consider outcome in terms of HRQoL and functional outcome following repair of ruptured AAA remains largely uncertain. If survivors of ruptured AAA were returned to a significant level of functional disability despite a near-normal life expectancy, the benefit of intervention becomes less apparent. Indeed, an intervention that encompasses a postoperative quality of life that will be unacceptable to the patient may be regarded as futile [213]. This concept has important implications where a selective policy in the management of ruptured AAA is employed; it could be argued that quality-adjusted survival rather than absolute survival should be used to guide operative selection [200].

Current evidence suggests that the majority of survivors of RAAA may expect to regain their preoperative quality of life. However, a proportion will experience postoperative deterioration of their functional status. No reports exist to inform

whether postoperative functional outcome can be correlated to preoperative risk factors. The ability to predict patients at risk of impaired quality of life following repair of ruptured AAA may have significant implications in preoperative patient selection. Prospective studies with larger sample sizes are needed to clarify the HRQoL outcomes of survivors of ruptured AAA repair and identify variables predictive of functional disability.

1.14. Aims

This thesis aims to:

- Examine potential predictors of mortality and assess current peri-operative outcomes for ruptured AAA through retrospective study.
- Prospectively study patients presenting with ruptured AAA to determine novel and established preoperative predictors of outcome.
- Validate existing scoring systems on a prospective cohort of patients and devise a novel prognostic scoring instrument.
- Examine functional outcome status in patients who survive ruptured AAA repair.

2. Glasgow Aneurysm Score and Hardman Index

2.1. Introduction

It has been proposed that the only means by which to improve outcomes after open repair of ruptured AAA is to operate only on patients with reasonable operative risk. Similarly, situations exist where it may be futile or even unethical to perform surgery or to continue treatment in patients with prohibitive risk. However, no robustly validated methods exist by which to identify those patients predisposed to mortality following aneurysm repair and patient selection is frequently performed on the basis of subjective assessment criteria.

As described in Chapter 1, the Glasgow Aneurysm Score (GAS) and Hardman Index are two practicable, objective predictive scoring systems recommended for use in patients with ruptured AAA [111,115]. This study aimed to assess their validity on a contemporary series of patients from a single, high-volume centre.

2.2. Methods

All patients admitted to the Edinburgh Vascular Surgical Service for repair of AAA over a two-year period (January 2000 to December 2001) were identified from a prospective database and included in a retrospective observational study. The database, together with hospital records, provided demographic details, and clinical and operative information, for all patients undergoing attempted repair of ruptured AAA. Operation was defined as the delivery of an anaesthetic with the intention of performing AAA repair. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause for haematoma other than an aneurysm [214]. All patients were operated on by one of six consultant vascular surgeons. The GAS and Hardman Index were recorded for each patient and related to subsequent clinical outcome.

Methodology for the calculation of the Glasgow Aneurysm Score and Hardman Index have been described in Chapter 1 and may be also found in Appendix 1.

Statistical analysis was performed using SPSS for Windows Release 11.0.0 (SPSS Inc., Chicago, Illinois, USA). The receiver-operator characteristic (ROC) curve and Chi squared test for trend was used to evaluate the performance of the GAS and Hardman Index respectively in predicting postoperative death. Differences between groups for non-parametric continuous variables were determined by the Mann-Whitney *U* test; $P \leq 0.05$ was considered significant.

2.3. Results

One hundred patients were admitted with ruptured AAA during the study period. Of these, 18 (18%) patients were deemed unfit for aneurysm repair due to prohibitive co-morbidity. There were 11 men and seven women of median (range) age 81 (66-97) years. Eight patients had been previously assessed and deemed unsuitable for elective repair. Reasons for non-operative management are listed in Table 2.1. Median (range) GAS in patients who did not undergo operation was 102 (84-127). These patients, in general, were not subject to a full remit of baseline investigations on admission to allow accurate Hardman Index scoring.

The remaining 82 patients underwent attempted repair of ruptured AAA and are included in the present analysis. There were 68 men and 14 women of median (range) age 73 (54-87) years. Thirty (37%) patients died after operation while of all patients admitted to hospital with a ruptured AAA during the study period, 48 (48%) died.

Glasgow Aneurysm Score:

The GAS was a poor predictor of mortality after ruptured AAA repair. The mortality rates in terms of tertiles of GAS distribution are shown in Figure 2.1. The median (range) GAS was not significantly different in patients who survived operative repair and those who did not: 93 (57-125) *versus* 96 (71-115). Analysis of the ROC curve showed that the GAS had an area under the curve of 0.606 (95% C.I. 0.483 – 0.729; S.E. 0.063; P=0.112) for predicting perioperative death (Figure 2.2).

Hardman Index:

There was no significant association between Hardman Index score and operative mortality (P=0.211) (Table 2.2). Analysis of the ROC curve showed that the HI had an area under the curve of 0.599 (95%CI 0.478 – 0.719) for predicting perioperative death (Figure 2.2). Patients with no Hardman risk factors appeared to be at low risk with an operative mortality of 15 per cent. However, of nine patients with three or more Hardman risk factors, six survived aneurysm repair. The distribution of Hardman risk factors in this subgroup is shown in Table 2.3. Of the six survivors, four were discharged home, one was discharged to a spinal rehabilitation unit, due to perioperative cord ischaemia, and one was discharged to a community rehabilitation hospital. Median (range) survival in this group was 35.5 (1-53) months (Table 2.4).

Table 2.1. Primary reason for refusal of surgery in 18 patients.

Reason for refusal	Number of patients
Cardiorespiratory comorbidity	7
Cardiac arrest / Refractory LOC	3
Malignancy	3
Age related comorbidity	3
Dementia	2

LOC – Loss of consciousness

Table 2.2. Distribution and mortality rates in 82 patients according to Hardman Index.

Hardman Index	0	1	2	≥3
No. of patients	26 (32%)	31 (38%)	16 (20%)	9 (11%)
No. of deaths	4 (15%)	17 (55%)	6 (38%)	3 (33%)

Values in parentheses are percentages

Table 2.3. Distribution of risk factors in nine patients with three or more Hardman Index variables.

Hardman Index risk factor	**6 Survivors**	**3 Non-Survivors**
Age (years)	76 (66-86)	78 (76-81)
Loss of consciousness	1 patient	1 patient
Creatinine (μmol/l)	215 (136-498)	208 (203-263)
Haemoglobin (g/dl)	8.3 (7.5-16.3)	11.4 (9.6 -13.8)
ECG ischaemia	5 patients	2 patients

Values are median (range) unless otherwise stated

Table 2.4. Long-term survival following hospital discharge in six patients with three or more Hardman risk factors.

Patient	Status	Survival (months)
1	dead	1
2	alive	29
3	dead	33
4	alive	38
5	dead	44
6	alive	53

Table 2.5. Operative mortality according to Hardman index in four reported series.

	Hardman Index			
Series	0	1	2	≥3
Hardman *et al.* [4]	16%	37%	72%	100%
154 patients				
Prance *et al.* [7]	18%	28%	48%	100%
69 patients				
Neary *et al.* [12]	35%	55%	74%	90%
188 patients				
Boyle *et al.* [13]	8%	24%	55%	100%
79 patients				
Edinburgh	15%	55%	38%	33%
85 patients				

Figure 2.1. Postoperative mortality rates according to different tertiles of the Glasgow Aneurysm Score.

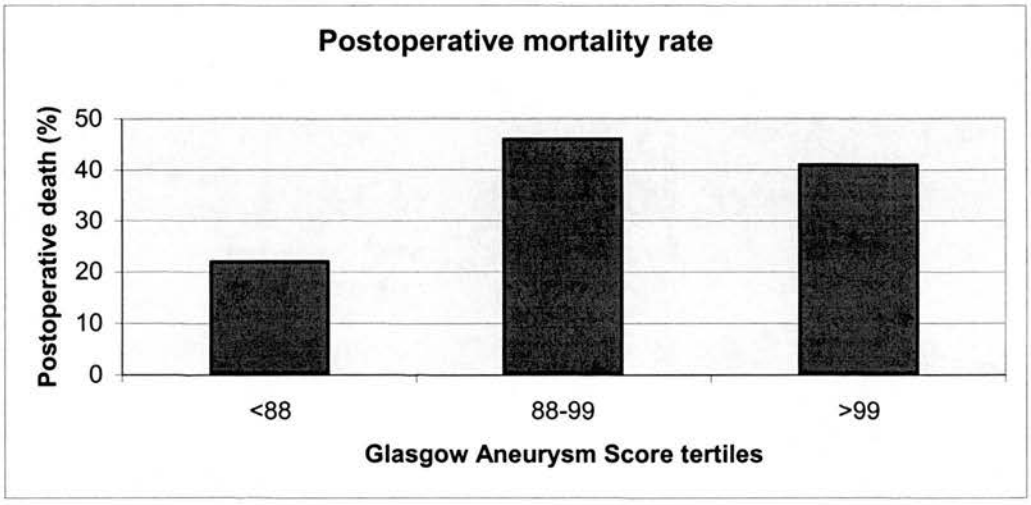
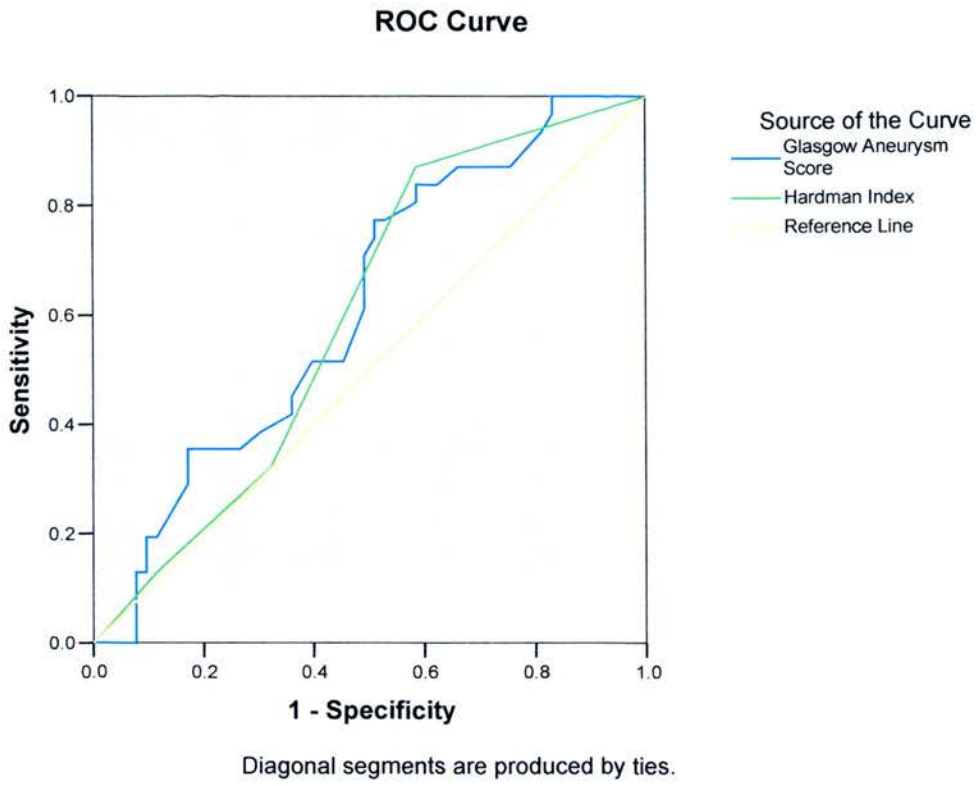


Figure 2.2. Receiver operator characteristic curve of Glasgow Aneurysm Score and Hardman Index and death



2.4. Discussion

Subjecting patients at extreme operative risk to futile attempts at repair of ruptured AAA has significant implications not only in terms of resource utilisation but also from an ethical standpoint. It is for these reasons that the majority of vascular surgeons in Great Britain and Ireland advocate the use of a selective policy in the management of patients with ruptured AAA [2]. A scoring system that could precisely identify patients with ruptured AAA in whom operative intervention would be unsuccessful would be a valuable tool for the practising vascular surgeon. To date such an instrument remains elusive. To deny operation to a patient based on an imprecise predictive tool would represent suboptimal practice. For this reason, any proposed scoring system requires comprehensive and robust validation.

From the present data, both the GAS and Hardman Index appear to lack validity. The GAS has recently been shown to demonstrate good validity when applied to elective AAA repair [215,216]. However, validation in patients with ruptured aneurysms is less robust. Samy and colleagues have previously reported on 92 patients with ruptured lesions from three centres [116]. They concluded that scores over 95 were associated with a mortality rate of 80%. From the present series, scores of 99 and more were associated with an approximately 40% operative mortality. Indeed, it is impossible to identify any score that confers extreme-risk and even in 14 patients with scores of 110 or more, operative mortality did not exceed 50 per cent. The Finnvasc Study Group have recently reported on a nine-year, retrospective series of 836 patients with ruptured AAA from 21 hospitals. This group showed the GAS to accurately predict

postoperative mortality, but were unable to distinguish a cut-off for patients at extreme risk [117].

The GAS was originally derived from an analysis of preoperative variables in patients with intact or ruptured AAA. Though it displays good-fit as a predictive tool for elective AAA repair, it seems to be less reliable when used solely in patients with ruptured aneurysms, as seen in the present series. Its poor performance not only questions its use in outcome prediction, but also as a risk-stratification tool for comparative audit of ruptured AAA mortality.

Until now, the Hardman Index has been reported to show good validity and has been recommended by four independent series (Table 2.5) [101,111-113]. Its appeal is heightened by its simplicity and ease of use. It has been unanimously concluded that the presence of three or more Hardman risk factors in a patient, represents a uniformly fatal prognosis. Combining these four series, of 32 patients with three or more positive variables who underwent attempted aneurysm repair, all died apart from one patient who survived to hospital discharge but succumbed six-weeks later in a nursing home.

It is surprising that both scoring systems display such poor performance in the current data. If the Hardman Index had been utilised as a means of selecting patients for operation in the present series, six patients would have been denied life saving operation. This is particularly alarming as four of these patients were successfully discharged back to their home environment. There are several possible reasons for

such a discrepancy compared to the previous series. Though the present data are retrospective and susceptible to bias, so too are three of the four former reports that have attempted to validate the Hardman Index. The current series reports from a single high-volume centre, on consecutive patients operated on by a group of six surgeons during a contemporary two-year study period. The operative mortality from the current series is consistent with that regularly reported from our centre for ruptured AAA repair and may influence the under-performance of both the Hardman Index and GAS [214].

In contrast, preceding retrospective series have been drawn from prolonged study periods or reported on non-consecutive patients [111-113]. The two prospective evaluations available in the literature pooled data from multiple centres [101,116]. Furthermore, the relationship between hospital and surgeon-volume and improved outcome is established in elective aortic aneurysm repair and is likely to be present in ruptured AAA repair [217,218]. This may explain the superior performance of the GAS in the Finnvasc Study Group data; where the majority of centres operated on fewer than 10-ruptured aneurysms each year - high-risk patients may be more likely to survive when managed in a high-volume centre [117].

The findings from the present study question the validity of both the GAS and Hardman Index as predictive tools in patients with ruptured AAA. Both scoring systems do not accurately predict mortality in high-risk patients and neither can be recommended for routine use in clinical decision making. Further risk modelling

with prospective validation is required in order to identify accurately and objectively those patients in whom operative intervention may be inappropriate.

3. Edinburgh Ruptured Aneurysm Score

3.1. Introduction

Although the incidence of ruptured AAA is increasing in Europe, there is conflicting evidence on which variables may be used to inform outcome prediction in patients with ruptured AAA [8,101,145,219]. The previous chapter from this thesis has shown that the two most popular preoperative risk-scoring methods (Hardman Index and Glasgow Aneurysm Score) lack validity and this finding has now been confirmed by other centres [220,221]. Reasons for this lack of fit may be related to the fact that the existing models are derived from clinical data that are mostly two decades old and which were accumulated over long study periods. Furthermore, they include results from low-volume institutions. Their use cannot be recommended for the purpose of clinical decision-making. The present study aimed to examine preoperative variables associated with perioperative death in a large, contemporary series of patients from a high-volume centre.

3.2. Methods

All patients admitted to the Edinburgh Vascular Surgical Service who underwent repair of ruptured AAA over a 31-month period (January 2000 to July 2002) were identified from a prospective database and included in an observational study. The database, together with hospital records, provided demographic details, and clinical and operative information, for all patients undergoing attempted repair. Operation was defined as the delivery of an anaesthetic with the intention of performing AAA repair. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause for haematoma other than an aneurysm [214]. All patients were operated on by a group of seven vascular surgeons. Fifty-three preoperative variables, identified in other studies, or suspected on clinical grounds, to be associated with mortality, were recorded for each patient and related to subsequent outcome.

Loss of consciousness was defined as an in-hospital event and Glasgow Coma Scale (GCS) was defined as the best recorded level in hospital. Cardiac symptoms were typified by previous myocardial infarction, anginal symptoms or symptoms of congestive cardiac failure. Respiratory symptoms were defined by dyspnoea at rest or on exertion, and peripheral arterial disease was defined by a history of intermittent claudication or critical limb ischaemia. Electrocardiographic (ECG) ischaemia was typified by greater than 1 mm ST segment depression or an associated T-wave change on the admission ECG.

Statistical analysis was performed using SPSS for Windows Release 13.0.0 (SPSS Inc., Chicago, Illinois, USA). Univariate differences between categoric variables were compared using the chi-squared test with Yate's correction or Fisher's exact test. Univariate differences between groups for parametric and non-parametric continuous variables were determined by the unpaired student-t test and Mann-Whitney *U* test respectively. $P \leq 0.05$ was considered significant. Multivariate modelling examining the simultaneous and independent effect of the significant demographic and clinical characteristics was then carried out using logistic regression. Variables significant at the 10% level on univariate analysis were included in the multivariate model. A stepwise (forwards–backwards) variable selection procedure was adopted. Clinically relevant variables predictive of death were then modeled to develop a prognostic risk score for ruptured AAA. The chi-squared test for trend was used to compare the trend in actual mortality rate as related to increasing risk score.

3.3. Results

One hundred and twenty-nine consecutive patients were admitted with ruptured AAA during the study period. Of these, 105 (81%) underwent attempted open repair and 24 (19%) were deemed unsuitable for operation due to prohibitive co-morbidity. Of the 105 patients undergoing attempted open repair, 91 were men and 14 were women. The mean (SD) age of the study population was 72 (7) years. Forty-seven (45%) patients were transferred from another hospital and the remainder were referred directly to the vascular surgical service by their general practitioner, the Emergency Department or by another specialty within our institution.

Nineteen patients required a secondary intervention following their aneurysm repair. Twelve (58%) of these patients needed a further laparotomy for haemostasis, three (16%) needed colonic resection and five (25%) needed some other form of intervention; one patient required two secondary interventions. There were 39 (37%) deaths in-hospital or within 30-days of operation. Sixteen (41%) of these patients died during surgery of massive haemorrhage or cardiac arrest. Eighteen (46%) died of multiorgan failure, and five (13%) died of other causes. Of 66 surviving patients, 61 (92%) suffered one or more postoperative complications as defined by the Committee on Reporting Standards of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery [222].

Preoperative variables predictive of death after attempted repair of ruptured AAA are listed in Tables 3.1 and 3.2. Of the continuous variables only haemoglobin and blood pressure were predictive of perioperative death. These continuous variables were

stratified to create categoric variables for further univariate analysis. Of all categoric variables, loss of consciousness, cardiac arrest, haemoglobin of <9g/dl, BP<90mmHg and GCS <15 were associated with perioperative death. However, loss of consciousness and cardiac arrest were observed in only eight and five patients respectively.

On logistic regression analysis of these five variables, none reach significance at the 5% level. Exclusion of the variables loss of consciousness and cardiac arrest yields the multivariate model seen in Table 3.3. The remaining variables were retained to determine the cumulative effect of multiple risk factors in a scoring system. With risk factors equally weighted, three probands of risk were established (Table 3.4). There was a significant association between actual mortality and cumulative risk factors (P=0.003).

Table 3.1. Univariate analysis of preoperative continuous variables

Variable	Number of missing cases	Mean (SD) or median (range) of survivors	Mean (SD) or median (range) of non survivors	P value
Age		71.9 (7.4)	73.6 (6.7)	0.250
Duration of symptoms (h)	6	6 (0-240)	4 (1-72)	0.218
Haemoglobin (g/dl)	**1**	**12.0 (2.5)**	**10.7 (3.1)**	**0.038**
White cell count ($x10^9$/l)	1	13.8 (6.5-33.7)	13.8 (5.2-31.1)	0.989
Platelets ($x10^9$/l)	3	195 (90-569)	207 (71-522)	0.353
Prothrombin time (s)	23	10 (8-31)	11 (9-62)	0.256
APTT*(s)	25	32 (24-52)	32 (24-210)	0.206
Fibrinogen (g/l)	25	3.5 (1.5)	3.2 (1.5)	0.386
Urea (mmol/l)	1	7.6 (3.2-10.3)	7.0 (3.2-13.7)	0.688
Creatinine (μmol/l)	1	124 (78-498)	141 (84-263)	0.169
Albumin (g/l)	20	36 (19-51)	35 (17-45)	0.118
Sodium (mmol/l)	1	138 (124-148)	139 (122-148)	0.089
Potassium (mmol/l)	1	4.0 (0.7)	4.0 (0.5)	0.996
Alanine Transaminase (u/l)	20	14 (6-221)	12 (5-154)	0.205
Highest pulse rate (bpm)	9	95 (55-190)	99 (60-130)	0.794
Lowest BP (mmHg)	**5**	**80 (50-165)**	**73 (0-135)**	**0.003**
Highest BP (mmHg)	**10**	**150 (33)**	**135 (36)**	**0.049**

*Activated Partial Thromboplastin Time

Table 3.2. Univariate analysis of preoperative categoric variables

Variable	Number of missing cases	Number of observations (Survivors)	Number of observations (Non survivors)	P value
Age >=75 years		24	20	0.196
Female sex		8	5	1.000†
Inter hospital transfer		28	19	0.672
Loss of consciousness	**6**	**2**	**6**	**0.022†**
Cardiac arrest		**0**	**5**	**0.006†**
ECG ischaemia	7	22	16	0.313
Hb <9g/dl	**1**	**7**	**11**	**0.038**
Creatinine >190 μmol /l	1	8	3	0.742
BP <90mmHg	**5**	**33**	**29**	**0.036**
GCS <15	**5**	**14**	**17**	**0.016**
Diabetes	5	4	0	0.310†
Cardiac symptoms	6	24	12	0.921
Respiratory symptoms	4	30	17	1.000†
Peripheral arterial disease		4	7	0.095†
Previous vascular intervention		0	1	0.371†
Warfarin therapy		0	2	0.136†
Beta blocker therapy		19	8	0.480
Steroid therapy		2	1	1.000†
Anti-platelet therapy		32	15	0.710
Anti-anginal therapy		10	3	0.363†
Preoperative inotropes		1	3	0.143†

† Fisher's exact test

Table 3.3. Multivariate model of variables related to perioperative death

Variable	**P value**	**Odds ratio**	**95% Confidence interval**
Haemoglobin <9g/dl	0.102	2.519	0.831-7.630
BP < 90mmHg	0.148	2.020	0.779-5.241
GCS < 15	0.077	2.318	0.916-5.866

Table 3.4. Mortality of patients with three equally weighted risk factors (Haemoglobin <9g/dl, BP<90mmHg, GCS <15) according to number of factors present.

Variable	Number of patients	Number of deaths	Percentage mortality
≤ 1	70	20	29%
2	30	15	50%
3	5	4	80%

3.4. Discussion

Many authors have attempted to identify preoperative variables that predict outcome and which might define the group of patients at extreme risk who would not benefit from operation after AAA rupture. However, there has been little consistency in reported findings and poor reproducibility among differing patient populations. Furthermore, data from the preceding chapter showed that two well-established scoring systems, the Hardman Index and the Glasgow Aneurysm Score, widely held to be credible instruments in risk prediction, lack validity. There are several possible reasons for the poor performance of the present data, when applied to existing scoring models. In contrast to much of the existing data, the present series represents a large number of patients accumulated over a short contemporary study period and operated on exclusively by a small group of specialist vascular surgeons. This is likely to minimise some of the bias associated with other retrospective analyses.

These data come from a high volume tertiary unit serving a Scottish population of approximately 1 million individuals. Scoring systems will always reflect the specific population and study period from which they were designed and modelled. For this reason, although a scoring system may hold true for one population, it must not be assumed to do so for other populations without appropriate, and ongoing, validation [223]. While it may be argued that the current data are vulnerable to selection bias, as some patients were palliated and not subjected to attempted operation, there is no other ruptured AAA risk scoring system that has been modelled on patients treated by a specialist vascular service over the last decade.

Of the well-known predictive instruments for ruptured AAA, all include age as a risk factor. In contrast, age was not found to be a significant risk factor in the present series. Age may be considered an indirect marker of physiological status, and from these data seemed to lack sensitivity as a predictor of adverse outcome. However, it may also be considered surprising that renal function, as represented by serum creatinine, was not identified as a predictive variable when it too is included in both the Hardman and Glasgow scores. Preoperative creatinine >130μmol/l is recognised as a perioperative risk factor for adverse outcome in non-cardiac surgery [224]. However, overall median (range) creatinine in the current series was 129 (78-498) μmol/l. This may imply that the majority of patients with ruptured AAA had evidence of preoperative renal dysfunction and so creatinine might lack predictive value in this circumstance. Review of existing literature reveals much conflicting data and there is no consensus on the usefulness of creatinine as a risk factor for perioperative death.

From the present data, the goal of a scoring system that can accurately predict all patients in whom attempted repair will prove futile seems unrealistic. Although five significant risk factors were identified on univariate analysis, these all failed to retain significance at the 5% level when subjected to multivariate modelling. Of the five, in-hospital loss of consciousness and cardiac arrest may be disregarded as useful predictive variables because of their low observed frequency. The two were only observed in eight and five patients respectively and are vulnerable to a type I error. Preoperative loss of consciousness was associated with death in six of the eight patients and cardiac arrest was invariably associated with death; a naturally intuitive

finding. However, previous work has shown that unconsciousness and cardiac arrest are not always fatal after aneurysm rupture [158,172]. Although they have been frequently cited as useful risk factors predicting death after ruptured AAA, and one is a component of the Hardman Index, it is unlikely that there is any single preoperative variable that in isolation can predict unsuccessful outcome across different patient populations.

The remaining three variables noted on univariate analysis were retained for analysis in a multivariate model. Alhough they all lose significance at the 5% level, there is a trend to significance at an alpha level of 10%. The variables of haemoglobin <9g/dl, shock (BP<90mmHg) and GCS <15 are sensitive markers of physiological condition - haemoglobin level and blood pressure being directly proportional to tissue oxygen delivery, and GCS an indicator of adequate cerebral perfusion. All three variables have odd ratios of approximately two. When applied to an equally weighted, cumulative model of risk scoring, there are three clearly identifiable tiers of risk. Although even the most extreme band of risk is still associated with a 20% chance of survival, the instrument provides a useful method of assigning patients to a low, medium or high risk category prior to attempted operation. Furthermore, all three variables in the proposed model can be measured within a few minutes of a patient's arrival in the emergency department. The risk score can then be used to inform patients, and relatives, objectively of their illness severity and operative risk.

These data represent a novel predictive risk model for patients with ruptured AAA from a single UK tertiary centre. Though this instrument cannot be recommended

for use in patient selection at present, its potential utility in comparative audit and supporting clinical judgement warrants further prospective validation.

4. Validation of Scoring Systems

4.1. Introduction

The Glasgow Aneurysm Score (GAS), Hardman Index, and Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) risk equations are predictive scoring systems recommended for use in patients with ruptured AAA [111,115,118]. A previous chapter in this thesis describes the Edinburgh Ruptured Aneurysm Score (ERAS), a further novel prognostic index that, in contrast to other scores, was derived from a contemporary dataset. However, none of these scoring systems have been adequately validated to be of use in dictating therapy or justifying clinical decision-making.

This prospective study examined preoperative variables predictive of death after AAA rupture and assessed the validity of existing scoring systems.

4.2. Methods

Local Research Ethics Committee approval was obtained for this research. All patients admitted to the Edinburgh Vascular Surgical Service for repair of a ruptured AAA over a two-year period (August 2002 to December 2004) were included. Operation was defined as the delivery of an anaesthetic with the intention of performing AAA repair. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause for haematoma other than an aneurysm [214]. All patients were operated on by a group of five consultant vascular surgeons. Fifty-three preoperative variables, identified in other studies, or suspected on clinical grounds, to be associated with mortality, the GAS, Hardman Index V-POSSUM and RAAA-POSSUM (physiology only) scores and ERAS were recorded for each patient and related to subsequent clinical outcome. Surgical intervention was generally not undertaken if the patient declined operation, if the patient had a known serious comorbidity such as advanced malignancy, or if the patient was otherwise unsuitable, such as refractory loss of consciousness or cardiac arrest, severe dementia or poor functional status.

Methodology for the calculation of the Glasgow Aneurysm Score, Hardman Index and POSSUM scores have been described in Chapter 1 and may also be found in Appendix 1. The ERAS is decribed in the preceding chapter and is also found in Appendix 1.

Statistical analysis was performed using SPSS for Windows Release 13.0.0 (SPSS Inc., Chicago, Illinois, USA). The receiver-operator characteristic (ROC) curve and

Chi squared test for trend was used to evaluate the performance of the GAS, Hardman Index and ERAS in predicting postoperative death. POSSUM predicted mortality was compared by means of the chi-squared test, using the methods described by Hosmer and Lemeshow as appropriate [225]. $P \leq 0.05$ was considered significant.

4.3. Results

One hundred and eleven patients were admitted with ruptured AAA during the study period. Of these, 27 (24%) patients were deemed unfit for aneurysm repair due to prohibitive co-morbidity. There were 17 men and 10 women of median (range) age 79 (58-92) years. Reasons for non-operative management are listed in Table 4.1. Risk scores (GAS, HI, V-POSSUM and RAAA-POSSUM mortality scores and ERAS) in the 11 patients who were turned down for surgery on the basis of comorbidity (apart from malignancy) are shown in Table 4.2.

The remaining 84 patients underwent attempted repair of ruptured AAA and are included in the present analysis. There were 74 men and 10 women of median (range) age 73 (53-87) years. Thirty-seven (44%) patients died after operation while of all patients admitted to hospital with a ruptured AAA during the study period, 63 (57%) died. (One patient who did not undergo attempted repair survived her ruptured AAA and was discharged to a nursing home.)

Glasgow Aneurysm Score:

The mortality rates in terms of tertiles of GAS distribution are shown in Figure 4.1. The GAS was statistically related to mortality after attempted repair of ruptured AAA. The median (range) GAS was significantly lower in patients who survived operative repair than those who did not: 90 (61-127) *versus* 99 (66-126) (P=0.027). Analysis of the ROC curve showed that the GAS had an area under the curve of 0.64 (95% CI 0.52-0.76) for predicting perioperative death (Figure 4.2).

Hardman Index:

There was a significant association between HI score and operative mortality (P=0.010) (Table 4.3). Analysis of the ROC curve showed that the HI had an area under the curve of 0.685 (95%CI 0.568 – 0.802) for predicting perioperative death (Figure 4.2).

Edinburgh Ruptured Aneurysm Score:

There was a significant association between ERAS score and operative mortality (P<0.001) (Table 4.4). Analysis of the ROC curve showed that the ERAS had the largest area under the curve of 0.72 (95%CI 0.61-0.83) for predicting perioperative death (Figure 4.2).

POSSUM:

There was a significant association between POSSUM physiology score and operative mortality (P=0.002). ROC curve analysis showed that the physiology score had an area under the curve of 0.70 (95%CI 0.59 – 0.82) for predicting perioperative death (Figure 4.2). Table 4.5 shows the predicted risk of death and observed mortality rate for each of the POSSUM models used. The V-POSSUM (physiology only) model did not demonstrate a lack of fit (P=0.086). However, the RAAA-POSSUM (physiology only) model demonstrated a significant lack of fit (P=0.009).

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Table 4.1. Primary reason for refusal of surgery in 27 patients.

Reason for refusal	Number of patients
Cardiac arrest / Refractory LOC	13
Cardiorespiratory comorbidity	6
Age related comorbidity	5
Patient wishes	2
Malignancy	1

LOC – Loss of consciousness

Table 4.2. Risk scores in 11 patients who were palliated due to comorbidity.

Patient	Reason for palliation	Age	GAS	HI	V-POSSUM mortality (%)	RAAA-POSSUM mortality (%)	ERAS
1	Cardiac dysfunction, suprarenal AAA	73	107	0	41	70	1
2	Cardiac dysfunction, suprarenal AAA	79	96	1	38	67	1
3	Cardiac dysfunction, chronic renal failure	83	121	3	88	91	2
4	Cardiac dysfunction	87	111	4	88	91	3
5	Cardiac dysfunction, chronic renal failure	89	120	3	57	77	2
6	Severe chronic obstructive pulmonary disease	80	97	1	31	63	1
7	Previous disabling stroke	71	120	2	79	87	2
8	Preexisting severe brain injury	76	100	1	31	63	2
9	Severe dementia	76	110	2	45	72	2
10	Extreme age	92	116	2	71	83	3
11	Extreme age	92	119	1	15	49	2

Table 4.3. Distribution and mortality rates in 84 patients according to Hardman Index.

Hardman Index	0	1	2	≥3
No. of patients	21 (25%)	34 (40%)	18 (21%)	11 (13%)
No. of deaths	6 (29%)	11 (32%)	12 (67%)	8 (73%)

Values in parentheses are percentages

Table 4.4. Distribution and mortality rates in 84 patients according to Edinburgh Ruptured Aneurysm Score.

Edinburgh Ruptured Aneurysm Score	<1	2	3
No. of patients	46 (55%)	27 (32%)	11 (13%)
No. of deaths	12 (26%)	16 (59%)	9 (82%)

Values in parentheses are percentages

Table 4.5. Predicted and observed mortality according to V-POSSUM (physiology only) and RAAA-POSSUM (physiology only) models

	Range % predicted risk	Mean % predicted risk	No. in range	Predicted mortality	Observed mortality	Chi^2	Overall result for each model
	0-31	16	44	7	13	6.61	
	31-50	42	17	7	7	0.01	
SUM	50-70	59	12	7	9	1.21	
	70-100	80	11	9	8	0.32	
	0-100	36	84	30	37		Chi^2=8.16, P=0.086 (4df)
	0-55	41	31	13	9	1.91	
	55-70	63	23	15	8	8.13	
AA-SUM	70-80	75	15	11	9	1.73	
	80-100	86	15	13	11	1.86	
	0-100	61	84	51	37		Chi^2=13.63, **P=0.009** (4df)

Figure 4.1. Postoperative mortality rates according to different tertiles of the Glasgow Aneurysm Score.

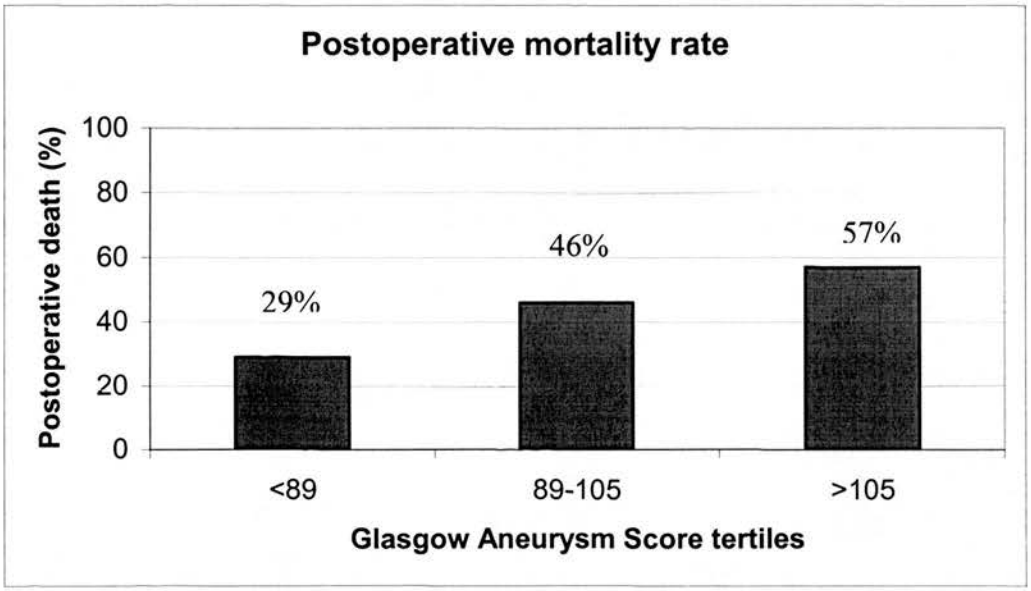
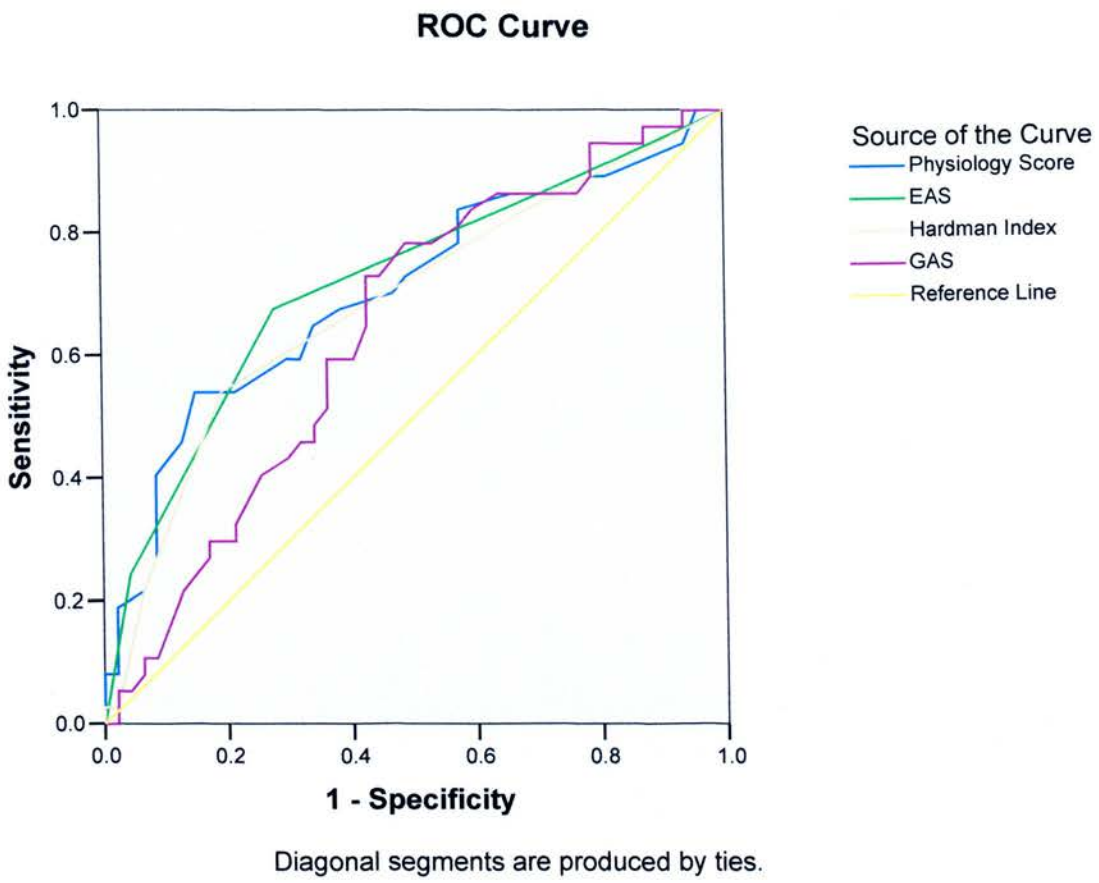


Figure 4.2. Recciver operator characteristic curve of Hardman Index, Glasgow Aneurysm score, Edinburgh Aneurysm Score and POSSUM physiology score and death



4.4. Discussion

Although there have been several attempts to devise a prognostic score with which to predict outcome in patients with ruptured AAA, few have undergone robust validation. An earlier chapter has shown from retrospective data, that two of the most well known scoring systems lack validity. The use of an imprecise predictive tool to justify clinical-decision making is open to question.

The GAS was derived from an analysis of preoperative variables in patients with intact or ruptured AAA admitted to general surgical units in Glasgow in the 1980s [115]. Previous validation of this instrument has come from prospective data on 92 patients pooled from three Scottish centres, retrospective data on 836 patients from the multi-centre Finnvasc database, retrospective data on 181 patients from a tertiary vascular centre in Rome and 84 patients from our own institution [116,117,221]. Apart from the Edinburgh data, the other datasets commend the GAS for its predictive power and validity. The Italian data described an area under the curve on ROC analysis of >0.9 whereas the Finnvasc group reported an area under the curve of 0.75 [117,221]. Interestingly, the more recent data from Rome noted that no patient with a GAS of >100 survived while the Finnish data describe a mortality rate of approximately 80% for patients with a score of >98 [117,221]. Similarly, the original Glasgow authors reported that scores of >95 were associated with a mortality rate of 80% [116].

The present prospective data contradict the findings of these three previous series. Though the GAS was statistically associated with mortality, the observed area under

the curve of 0.641 is much more modest and supports our previously reported retrospective data. Though the GAS does appear to perform better in the current prospective series, it does not appear to stratify patients into useful tiers of risk. Patients with scores of <90 are at low risk, but it appears difficult to identify the group of most interest; those patients at extreme-risk. Of the 19 patients with a score of 110 or more, only 11 (58%) died. Reasons for the contrasting performance of the GAS when applied to our data have already been described. The majority of the preceding data stemmed from low-volume institutions that operated on fewer than 20-ruptured AAA patients each year. It seems likely that the relationship between hospital and surgeon-volume and improved outcome is likely to play a significant part [179, 226].

The Hardman Index is, perhaps, the most well-known predictive instrument in patients with ruptured AAA. To date, including data from this thesis, there have been 10 series examining validity; only one has been prospective [101,111-114,220,221,227,228]. Initial reports and consensus was that the Hardman Index accurately predicted mortality after ruptured AAA. The presence of 3 or more variables was widely held to be fatal [101,112]. However, more recent data have shown that the instrument may not perform as well as initially reported, and that the presence of 3 or more variables is not always associated with death [220,227,228]. The present prospective data confirm that the Hardman Index may not display as convincing validity as initially reported. Though increasing score is associated with death, its predictive ability is, again, only moderate with an area under the curve of 0.684; less than previously reported. Patients with none or 1 positive variable were at low-risk with an observed mortality

of approximately 30% for both groups. However, the Index does not clearly identify the group of patients who are at extreme-risk. Of 11 patients with three or more variables, only eight (73%) died, while of the 18 patients with 2 variables, 12 (67%) died. These data confirm that the score cannot define a group of patients in whom attempted operation is futile. The merits of the present data are not only its prospective nature, but the fact that only one patient had an incomplete set of scoring data. In the existing literature, data have been unavailable for up to 42% of patients [228]. Indeed, in the only other reported prospective study, data were missing on almost a third of patients [101].

The POSSUM score is a tool that was designed to support comparative audit. It is important to recognize that it is not recommended for the prediction of outcome. There has been no prospective validation of the POSSUM risk equations recommended for vascular surgery when applied to patients with ruptured AAA. Of the existing retrospective literature, both the RAAA-POSSUM and V-POSSUM equations were shown accurately to predict risk when applied to preoperative data on 191 patients from Gloucester [113]. From the present preoperative data, both equations do not perform well, though only the RAAA-POSSUM model demonstrated a significant lack of fit. The RAAA-POSSUM model over predicted risk while the V-POSSUM model tended to under predict risk at the lower bands of predicted risk. This lack of fit raises concerns about its use as a risk-stratification tool for comparative audit of ruptured AAA mortality. Reasons for the discrepancy are unclear but further validation of this model is clearly needed. Nevertheless, the

complex nature of POSSUM risks equations, and the need to obtain 12 different variables renders the score less practicable for use in the acute setting.

The ERAS was modelled on retrospective data from patients presenting to our institution with ruptured AAA over a two-year period. It has had no internal or external validation and cannot be recommended for clinical use at present. When applied to the present data, the score was significantly associated with perioperative death. The appeal of this scoring system is its simplicity and the ease with which the 3 components of the score can be obtained and applied, even haemoglobin concentration can be rapidly assessed using point of care testing. Furthermore, as observed on the intitial dataset, three tiers of risk were discernible. None or one variable was associated with an approximately 30% risk of death while the presence of all three variables was associated with an 80% risk. Two variables were associated with an intermediate risk of between 50-60%. The limitations of this scoring system are acknowledged. It has been specifically modelled on a unique dataset and may not be applicable or show validity on external data.

These are the first prospective data to evaluate comprehensively the main scoring instruments recommended for use in ruptured AAA repair. The GAS and HI both did not perform as well as predictive instruments as reported previously. Furthermore, the V-POSSUM and RAAA-POSSUM also did not demonstrate compelling validity when applied to these data. The ERAS is an easily applied scoring system that allows patients to be quickly allocated to a low, medium and high-risk of perioperative

death. However, it does not enable the prediction of surgical futility. Further external assessment is required in order to confirm its validity.

5. Myocardial Injury

5.1. Introduction

Death and postoperative morbidity in patients who undergo technically successful repair of a ruptured aneurysm are generally attributed to the development of multiorgan failure, thomboembolic events and myocardial infarction [62]. Nevertheless, myocardial injury remains a frequently under recognised complication in the perioperative period.

Cardiac troponin I (cTnI) is a highly sensitive and specific marker for myocardial injury. In surgical patients cTnI has been shown to identify perioperative myocardial infarction (MI) more accurately than the conventional creatinine kinase-MB fraction isoenzyme [229]. In non-surgical patients with acute coronary syndromes, even small elevations of cTnI are associated with an increased risk of mortality and reinfarction [230,231]. However, the implications of perioperative myocardial injury in terms of clinical outcome and its role as a risk-stratification and prognostic tool are uncertain. It is unclear whether perioperative myocardial injury after emergency aortic surgery, diagnosed on the basis of cTnI, confers the same prognostic implications as traditional markers of myocardial infarction.

This study examined the relationship between early perioperative myocardial injury, as detected by elevated serum cTnI, and clinical outcome after repair of ruptured AAA.

5.2. Methods

Local Research Ethics Committee approval was obtained for this study. Patients undergoing attempted operative repair of ruptured AAA over a 22-month period (October 2002 to July 2004 inclusive) and who survived for more than 24h were included in a prospective observational cohort study. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause of haematoma other than an aneurysm[214]. Demographic and clinical variables for all patients were recorded. Preoperative cardiac and postoperative physiological risk stratification was carried out using the Detsky cardiac risk index and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score respectively [232,233]. All patients were operated on by a group of five consultant vascular surgeons.

Blood was sampled for cTnI on the patients' admission to the emergency room and on the first and second days after operation. These time points were chosen as representing the period of greatest risk of cardiac complications after vascular surgery [234]. Samples were collected in sterile, lithium heparin tubes (Sarstedt AG & Co. Nümbrecht, Germany) and analysed in the Clinical Biochemistry Laboratory of the Royal Infirmary of Edinburgh. Sample analysis was performed with an automated immunometric assay (Ortho-Clinical Diagnostics, Amersham, Bucks, UK). The 10% coefficient of variation level was 0.3 μg/L.

Primary outcomes assessed were postoperative mortality, defined by death in-hospital or within 30-days of operation, and perioperative cardiac dysfunction.

Cardiac dysfunction was determined on the following clinical and electrocardiographic grounds: prolonged cardiac chest pain, signs or symptoms of congestive heart failure, and electrocardiographic changes indicating ischaemia or a new persistent arrhythmia. Echocardiography was performed only when clinically indicated. Secondary outcomes included duration of mechanical ventilation, duration of critical care unit stay (intensive care unit or high dependency unit), and total hospital stay.

Statistical analysis was performed using SPSS for Windows Release 11.0.0 (SPSS Inc., Chicago, Illinois, USA). Univariate analyses between groups were determined by χ^2 or Fisher's exact test for categoric variables and Mann-Whitney *U* test for non-parametric continuous variables; $P \leq 0.05$ was considered significant.

5.3. Results

Eighty consecutive patients were admitted with ruptured AAA during the study period. Of these, 62 (78%) underwent attempted open repair and 18 (22%) were deemed unsuitable for operation due to prohibitive co-morbidity. Of the 62 patients undergoing operation, 11 (18%) died during surgery and one (2%) died soon after admission to the intensive care unit. Preoperative cTnI levels were normal in these 12 patients. The remaining 50 (80%) patients survived for 24h or more and all but one survived for more than 48h. There were 44 men and six women of median (range) age 71 (53-87) years. Forty-two (84%) patients had a contained retroperitoneal rupture and eight (16%) had free intraperitoneal blood at laparotomy. Twelve (24%) patients required temporary cross clamping of the suprarenal aorta while the remainder were managed with control of the infrarenal aorta. Thirty-eight patients (76%) had an aortic tube graft inserted and 12 (24%) required a bifurcated graft. No patient was dialysis dependent before operation but 19 (38%) had evidence of pre-existing renal insufficiency (serum creatinine >150μg/L) on admission.

Twenty-three (46%) patients had a detectable cTnI level at one or more time points during the first 48h after operation. Of these, only two (4%) patients had an elevated cTnI on admission, both of whom had a preoperative serum creatinine >150μg/L. Twenty-two (96%) of the 23 patients had elevated cTnI levels by the first postoperative day. There were no significant differences in Detsky cardiac risk index or APACHE II scores between patients with, and without, a perioperative cTnI elevation. The distribution of demographic and clinical variables between both groups is shown in Table 5.1.

Of the 23 patients with an elevated cTnI, 11 had clinical or electrocardiographic evidence of acute cardiac dysfunction during the first 48h after operation. The remaining 12 did not have any clinically apparent cardiac events despite elevated cTnI levels. Patients with occult cardiac dysfunction had significantly lower median (range) cTnI levels than those with a clinically evident cardiac event (0.52 (0.28-1.65) μg/L *versus* 12.7 (1.31-67.5) μg/L; P<0.001).

Thirteen (26%) of 50 patients died in the postoperative period. Ten (77%) of the 13 had an elevated cTnI at one or more time points in the first 48h - five (45%) deaths in 11 patients with elevated cTnI and clinical evidence of a cardiac event, and five (43%) deaths in 12 patients with elevated cTnI but no apparent cardiac dysfunction. There were only three (11%) deaths in the 27 patients who had no perioperative elevation of cTnI, significantly fewer than both groups of patients with elevated cTnI levels (P=0.031 and P=0.043 respectively). Of these three deaths, one patient died on the fourth postoperative day from multi-organ failure, one on the 38th postoperative day from respiratory failure, and one on the 46th postoperative day from an aorto-enteric fistula. Causes of death are shown in Table 5.2.

Patients with elevated cTnI levels who survived spent a significantly longer period in the intensive care and high dependency units than those with no perioperative cTnI elevation (P=0.038). Total in-hospital stay and duration of mechanical ventilation were not significantly different between the two groups (Table 5.3).

Table 5.1. Demographic and clinical variables in 27 patients without and 23 patients with perioperative cardiac troponin I (cTnI) elevation.

Variable	cTnI -ve	cTnI +ve	P value
Female sex	3 (11%)	3 (13%)	0.834†
Age (years)	69 (53-87)	75 (63-82)	0.031*
Detsky cardiac index	15 (10-30)	15 (10-65)	0.147*
Preop. creatinine >150μg/L	6 (26%)	13 (57%)	0.013†
Suprarenal aortic clamp	4 (15%)	8 (35%)	0.183†
Blood loss (ml)	3000 (1325-8500)	4600 (1070-21000)	0.062*
Bifurcated graft	4 (15%)	8 (35%)	0.183†
APACHE II score	16 (18-33)	19 (10-30)	0.065*

Values are median (range) or number of patients (%)

* - Mann-Whitney *U* test; † - Fisher's exact test

Table 5.2. Causes of death in three patients without and 10 patients with perioperative cardiac troponin I (cTnI) elevation.

Cause of death	**cTnI -ve**	**cTnI +ve**
Multiorgan failure	1	7
Respiratory failure	1	3
Aortoenteric fistula	1	-

Table 5.3. Outcomes in 27 patients without, and 23 with, perioperative cardiac troponin I (cTnI) elevation.

Outcome	**cTnI -ve**	**cTnI +ve**	**P value**
Critical care stay –*Survivors and non-survivors*	3 (1-38)	6 (1-46)	0.031
Duration of ventilation – *Survivors and non-survivors*	1 (1-38)	2.5 (1-43)	0.008
Total hospital stay – *Survivors and non-survivors*	14 (4-56)	12 (1-58)	0.711
Critical care stay – *Survivors*	3 (1-11)	5 (1-42)	0.038
Duration of ventilation – *Survivors*	1 (1-5)	1 (1-38)	0.199
Total hospital stay – *Survivors*	14 (7-56)	18 (8-58)	0.202

Values are median (range) days

Mann-Whitney *U* test

5.4. Discussion

A previous non-consecutive series of selected patients undergoing ruptured AAA repair in this hospital had an incidence of perioperative myocardial injury in excess of 50% [76]. Present data confirm that around half the patients who survive repair of a ruptured AAA sustain a detectable perioperative myocardial injury. Of these, roughly half will have a clinically silent event, with low-level cTnI elevation. In comparison, approximately a quarter of the patients who undergo a major vascular surgical operation develop perioperative myocardial injury as determined by raised cardiac troponins [229]. The incidence of myocardial injury in critically ill patients on intensive care units is similarly reported to be between 15 and 40% [235-7]. It may be inferred that patients with ruptured AAA are subject to a greater risk of perioperative cardiac injury. This is likely to reflect the impact of massive haemorrhage and transfusion, compounded by the attendant burden of cardiovascular comorbidity that is common in this patient population. However, it is of interest to note in the present series that preoperative cardiac status, as assessed by the Detsky risk index, was not associated with postoperative myocardial injury. It is acknowledged that the sample size of this series does not permit a more meaningful multivariate analysis of perioperative variables associated with myocardial injury and outcome.

Cardiac troponins are recommended as the standard biomarker for the diagnosis of myocardial infarction and as a risk-stratification tool in patients with acute coronary syndromes [63,238]. Cardiac troponins may also be elevated in other clinical conditions and confer similar prognostic value in patients with sepsis, renal failure and pulmonary embolism [66]. It is now acknowledged that even minor elevations of

cardiac troponin, below the diagnostic criteria for myocardial infarction, are indicative of increased clinical risk [239]. The present series demonstrates that slight, clinically silent elevations of cTnI within the first 48h after operation confer an increased risk of postoperative death. In contrast, only one of 27 patients without a cTnI rise died within 30-days of operation. In terms of secondary outcomes, patients with raised cTnI also required significantly longer stays on the critical care unit. Though total hospital stay was not significantly different between patients with, and without, cTnI elevations, it is recognised that hospital stay, unlike critical care unit stay, may be influenced by circumstances unrelated to a patient's clinical condition.

Are raised cTnI levels a marker of the severity of the patients' critical illness and its consequent adverse outcome, or is there a causal relationship between myocardial dysfunction and subsequent morbidity and mortality? The proposed mechanisms of raised cardiac troponin, apart from myocardial necrosis, include leakage of cardiac proteins from myocyte cell membranes [66]. Tumour necrosis factor-α (TNF-α) is known to increase endothelial permeablility and may be implicated at the cardiac myocyte level too [240,241]. Patients who survive initial repair of ruptured AAA develop a postoperative systemic inflammatory response syndrome with associated elevation in circulating TNF-α [77,242]. It has been reported that high levels of TNF-α are associated with poor outcome after ruptured AAA repair. Thus, cTnI elevation and myocardial dysfunction may be an effect of an underlying systemic inflammatory response. In support of a causal association, most patients in the present series with a cTnI elevation had detectable levels within the first 24h after operation. Furthermore, organ dysfunction, as determined by postoperative APACHE II score, was not

associated with the development of cardiac injury. It is intuitive that any degree of myocardial dysfunction may compromise a patient's potential for recovery and be associated with prolonged critical care unit stays and adverse outcome. The correlation of raised cTnI levels and adverse outcome noted in different studies across a variety of patient subgroups, some with lesser potential for systemic inflammation, also favours a causal relationship [72,230,236,237]. Nonetheless, the interplay between systemic inflammation and perioperative myocardial injury requires further investigation.

The present study confirms that perioperative cardiac injury after ruptured AAA repair is common and often clinically silent. Even modest levels of cTnI elevation are predictive of short-term adverse outcome. Such a marker of increased risk in the early perioperative period may further inform clinical decision-making.

6. Systemic Inflammation

6.1. Introduction

Inflammation is an integral factor in the pathogenesis of abdominal aortic aneurysms (AAA), histologically characterised by a transmural infiltration of macrophages and lymphocytes. These cells are thought to elicit an inflammatory cytokine cascade, culminating in the degeneration of aortic connective tissue [37]. Interestingly, patients with AAA have elevated serum markers of inflammation and the acute phase response when compared with healthy controls and controls with coexistent vascular disease [84,85]. Furthermore, serum concentrations of inflammatory cytokines are associated with aneurysm diameter and rate of expansion [243]. However, the precise relationship between systemic markers of inflammation, the acute phase response and aortic aneurysms is uncertain.

C-reactive protein (CRP) is an acute-phase protein that is a strong, independent risk factor for atherosclerosis [80]. It may also predict survival in critically ill patients and patients with underlying neoplasia [87,88]. It is unclear whether inflammatory biomarkers have any such prognostic significance in patients undergoing AAA repair. Systemic inflammatory proteins may have a role as a diagnostic tool or as a means of preoperative risk-stratification.

This study compares easily measured preoperative inflammatory biomarkers in patients admitted for open repair of intact and ruptured AAA, and their relationship to clinical outcome.

6.2. Methods

Local Research Ethics Committee approval was obtained for this research. Consecutive patients admitted for open repair of intact or ruptured AAA were included in a prospective observational cohort study over a 20-month period (January 2003 – September 2004). Those with intact AAA were further stratified into an asymptomatic group undergoing elective repair, and an acutely symptomatic group requiring urgent operation. An acutely symptomatic aneurysm was typified by severe back and/or abdominal pain, haemodynamic stability and a tender AAA on palpation. Ruptured aneurysm was typified by the presence of retroperitoneal and/or intraperitoneal blood at laparotomy in the absence of any other identifiable cause other than an aneurysm[214]. Patients were diagnosed as having an inflammatory AAA by operative appearance. An inflammatory AAA was characterised by the presence of a thickened aneurysmal wall, perianeurysmal fibrosis and adhesions to adjacent structures[214]. Demographic and clinical variables for all patients were recorded. Preoperative physiological status was stratified according to the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) [118]. All patients were operated on by one of five consultant vascular surgeons.

Blood was sampled for the following biomarkers of inflammation: CRP, platelet count, white blood cell count, fibrinogen and albumin. Plasma samples were collected on the time of admission in sterile, lithium heparin, potassium EDTA, or sodium citrate tubes (Sarstedt AG & Co. Nümbrecht, Germany) and analysed in the Clinical Biochemistry and Haematology Laboratories of the Royal Infirmary of

Edinburgh. C-reactive protein analysis was performed with an automated immunoturbidimetric assay (Abbott TDX, Abbott Laboratories, Maidenhead, UK). A systemic inflammatory response was defined by a CRP level of >10mg/l [78]. Primary outcome was assessed in terms of postoperative mortality, defined as death in-hospital or within 30-days of operation.

Statistical analysis was performed using SPSS for Windows Release 13.0 (SPSS Inc., Chicago, Illinois, USA). Univariate analyses between groups were determined by chi-squared or Fisher's exact test for categoric variables and Kruskal-Wallis and Mann-Whitney *U* test for non-parametric continuous variables. Spearman's rank correlation coefficient was calculated to assess the strength of association between continuous variables. $P \leq 0.05$ was considered significant.

6.3. Results

Fifty-one consecutive patients (39 asymptomtatic and 12 acutely symptomatic) underwent attempted repair of an intact aneurysm, and 61 had repair of a ruptured aneurysm, during the study period. Demographic and clinical variables are shown in Table 6.1.

There was no statistically significant difference in age (P=0.876), gender (P=0.275), aneurysm diameter (P=0.871) or POSSUM physiology score (P=0.201) between patients with an asymptomatic or symptomatic intact AAA. Patients with ruptured AAA had larger aneurysms on selectively utilised computed tomography (CT) or ultrasound scan (P=0.007) and higher POSSUM physiology scores (P<0.001), than those with asymptomatic lesions; age (P=0.470) and gender (P=0.609) distribution were, however, similar.

There were no statistically significant differences in age (P=0.457), gender (P=0.257) or AAA size (P=0.197) between patients with ruptured AAA and those with symptomatic intact aneurysms; however, POSSUM physiology scores (P=0.001) were greater in the former group. No patient had clinical evidence of a significant coexistent inflammatory disease and the distribution of inflammatory AAAs, as determined at laparotomy, is shown in Table 6.1.

There were significant differences in CRP level, fibrinogen level, WBC count and platelet count across the three groups of patients (Table 6.2). Asymptomatic intact AAAs were associated with a lower CRP level (P<0.001), fibrinogen level (P=0.022)

and WBC count (P=0.036), and with a higher serum albumin (P=0.017) than symptomatic intact aneurysms; platelet counts were similar (P=0.152). Asymptomatic lesions were also associated with lower CRP level (P=0.002) and WBC count (P<0.001), and with higher serum albumin (P<0.001), than ruptured AAA. However, patients with asymptomatic AAA had greater platelet counts (P=0.026) and fibrinogen levels (P=0.005) than those with ruptured aneurysms.

Patients with symptomatic intact AAA had higher CRP levels (P=0.042) but a lower WBC count (P=0.04) than those with ruptured lesions. Platelet count (P=0.011) and fibrinogen levels (P=0.01) were higher with symptomatic intact aneurysms. There was no difference in serum albumin between groups (P=0.171). Analysis of all patients with AAA failed to demonstrate any correlation between age (r=0.139, P=0.157) or aneurysm size (r=0.010, P=0.930) and CRP. However, POSSUM physiology score correlated with CRP (r=0.283, P=0.004). The distribution of systemic inflammatory response as defined by serum CRP levels is shown in Table 6.3. Patients with symptomatic or ruptured AAA were more likely to have a systemic inflammatory response than asymptomatic patients (P<0.001).

There were three (8%), two (17%) and 21 (41%) perioperative deaths in the asymptomatic, symptomatic and ruptured AAA groups respectively. Causes of deaths are shown in Table 6.4. There was no statistically significant difference between survivors and non-survivors of AAA repair in terms of systemic inflammatory response, CRP level, WBC or serum albumin in any of the three

groups. Those who survived ruptured AAA repair had higher platelet counts (P=0.006) and serum fibrinogen levels (P=0.002) than those who died.

Table 6.1. Demographic and clinical variables in 112 patients undergoing open repair of AAA

	Asymptomatic AAA (n=39)	**Symptomatic AAA (n=12)**	**Ruptured AAA (n=61)**
Age (years)	72 (48-87)	71 (64-84)	72 (53-87)
Male sex	34 (87%)	9 (75%)	53 (87%)
POSSUM physiology score	19 (14-28)	23 (13-35)	33 (15-55)
AAA size (cm)	6.1 (4.7-10)	6.3 (3.4-9)	7.5* (4.5-10)
Inflammatory AAA	2 (5%)	0	1 (2%)

Values are median (range) or number (%)

* Selectively performed preoperative imaging

Table 6.2. Inflammatory biomarkers in 112 patients with AAA

	Asymptomatic AAA (n=39)	**Symptomatic AAA (n=12)**	**Ruptured AAA (n=61)**	**P value**
CRP (mg/L)	<5 (<5-22)	22 (5-103)	7 (<5-168)	<0.001
WBC $x10^9$/L	7.0 (4.4-13.7)	8.8 (5.4-19.2)	13.2 (4.4-24.0)	<0.001
Platelets $x10^9$/L	209 (125-320)	240 (123-428)	186 (89-462)	0.008
Fibrinogen (g/L)	3.6 (2.1-6.0)	4.6 (2.1-6.7)	2.8 (0.2-5.5)	<0.001
Albumin (g/L)	41 (34-47)	37 (27-47)	33 (18-47)	<0.001

Values are median (range). Kruskal-Wallis test

Table 6.3. Presence (CRP >10mg/) or absence (CRP ≤10mg/l) of a systemic inflammatory response in 36 asymptomatic patients and 70 symptomatic or ruptured AAA patients

	Asymptomatic AAA	**Symptomatic AAA**	**Ruptured AAA**
CRP≤10mg/l	31 (86%)	2 (18%)	32 (54%)
CRP>10mg/l	5 (14%)	9 (82%)	27 (46%)

Values are number (%).

Table 6.4. Causes of perioperative death in 30 patients

	Asymptomatic AAA	**Symptomatic AAA**	**Ruptured AAA**
Multiorgan failure	1	1	11
Intraoperative death	1	-	11
Myocardial infarction	1	-	2
Respiratory failure	-	1	1
Aorto-enteric fistula	-	-	1

6.4. Discussion

The systemic inflammatory response is typified by the synthesis of proteins by the liver [78]. The effect is mediated by proinflammatory cytokines. Proteins such as CRP and fibrinogen increase, while others such as albumin fall. Most AAAs exhibit features of inflammation on histological examination, and increased expression of local and circulating proinflammatory cytokines is well-documented in patients with aneurysms [43,82,83]. Controversy persists about the extent to which this cytokine up regulation evokes a systemic inflammatory response and about the influence of aneurysm symptomatology on this process [243].

This study shows that patients with symptomatic intact or ruptured AAA have elevated markers of systemic inflammation before operative intervention. Both CRP level and WBC were significantly higher than those encountered in patients with asymptomatic AAA. The stimulus for this inflammatory response is uncertain. Clearly, ruptured AAA causes acute haemorrhage and hypovolaemic shock as inflammatory triggers. However, symptomatic intact lesions do not result in such a profound physiological insult; a lower POSSUM physiology score reflects this. However, pain is a cardinal feature of inflammation and in acutely symptomatic AAA is thought to relate to a sudden expansion in aneurysm size [244]. This lesser trigger seems capable of evoking systemic changes in circulating inflammatory biomarkers too. This elevation of easily measured serum markers of inflammation supports their utility as diagnostic tools in patients with acute aortic pathology. While non-specific, their use in conjunction with clinical evaluation may prove a valuable indicator of impending or established aneurysm rupture. Interpretation of changes in

the other inflammatory markers is confounded by a number of factors. Acute blood loss and the dilutional and volume redistribution effects of intravenous fluid resuscitation may influence changes in platelet count and fibrinogen level [245]. The use of these inflammatory markers as diagnostic or prognostic tools is limited by such factors.

Despite similar physiological scoring, and the integrity of the aneurysm being preserved, patients with symptomatic lesions had an operative mortality rate more than twice that of patients undergoing repair of an asymptomatic AAA. Reasons for the increased operative mortality associated with symptomatic aneurysms, though well described, remain unresolved [246]. However, it is possible that elevated systemic inflammatory proteins in symptomatic patients may be implicated.

Multiple organ failure is a major cause of perioperative death after AAA repair [247]. Excessive activation of inflammatory pathways and release of inflammatory cytokines underpin organ dysfunction. An initial inflammatory stimulus, such as acute AAA expansion or rupture, may cause priming of inflammatory pathways. A subsequent stimulus, such as ischaemia-reperfusion injury during aneurysm repair, causes an inflammatory response greater than expected if it occurred in isolation [242]. Such a phenomenon might partly account for the increased mortality rates found in patients with acute AAA.

If a primed inflammatory response were related to perioperative death in patients with acute AAA, it would be anticipated that raised CRP levels would be associated

with death. However, the present data have shown that neither CRP level nor a systemic inflammatory response provide prognostic information in terms of survival after AAA repair. In contrast, Schillinger and colleagues have reported that admission CRP levels predict poor outcome [86]. Their retrospective series, combined patients with thoracic and abdominal aortic disease, including both aortic dissections and aneurysm. Despite the heterogeneity of their sample population, they concluded that CRP level was useful for risk prediction in acute aortic disease. The absence of such an association in the present series is surprising considering the positive correlation between preoperative physiological status, as reflected by POSSUM score, and CRP level (patients with greater physiological compromise had higher CRP levels). It is possible that the failure of CRP to predict mortality in the present data is a reflection of small sample size. Alternatively, the use of newer high sensitivity CRP assays may have yielded greater prognostic information. Furthermore, analysis of the temporal changes in inflammatory markers in the postoperative period may also have conferred useful prognostic information.

These data highlight the presence of an early elevation in inflammatory biomarkers and the systemic inflammatory response in patients before elective and emergency aortic aneurysm repair. This inflammatory process and upregulation of the acute phase response might affect perioperative outcome.

7. Functional Outcome

7.1. Introduction

The cost of ruptured abdominal aortic aneurysm (AAA) repair in financial terms and resource utilisation is significant [212]. Although survivors may return to a normal life expectancy, their functional outcome, in terms of health related quality of life (HRQoL), remains uncertain. In properly assessing the value of a surgical intervention, functional outcome must be examined alongside the more traditional outcome measures of operative morbidity and mortality. If a survivor of ruptured AAA was returned to a significant level of functional disability despite a near-normal life expectancy, the benefit of intervention would become less apparent. To quantify the efficacy of ruptured AAA repair with accuracy, HRQoL analysis is essential.

Published data on HRQoL after aneurysm rupture are limited. While it has been suggested that survivors of ruptured AAA repair regain their preoperative quality of life, this rests on retrospective data of uncertain validity [193-206]. This study examines the postoperative HRQoL of survivors of ruptured AAA repair when compared to that of patients undergoing elective AAA repair and of the general population.

7.2. Methods

Local Research Ethics Committee approval was obtained for this study. Patients undergoing open operative repair of a ruptured AAA over the 18-month period September 2002 to March 2004 were included in a prospective observational case-control study. Patients were selected for operative intervention and operated on by a group of five vascular surgeons. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause of haematoma other than an aneurysm at laparotomy. A control group of age and sex-matched patients undergoing elective open repair of asymptomatic AAA during the study period was also identified. Endovascular aortic repair was not utilised as a therapeutic option for either intact or ruptured AAA during the study period. Demographic and clinical variables for both groups were recorded. Severity of illness was scored using the Simplified Acute Physiology Score II (SAPS II) recorded during the first 24h after operation [182]. Patient survival was confirmed using hospital and general practice records.

The Short Form-36 Health Survey (SF-36) (QualityMetric Inc., Lincoln, Rhode Island, USA) is a generic HRQoL instrument and comprises 36 questions studying eight domains of health: physical functioning, social functioning, role limitations due to physical problems, role limitations due emotional problems, mental health, pain, vitality and general health perception. Each domain scores from 0 to 100, with higher scores representing a better quality of life. The reliability, validity and consistency of the SF-36 have been confirmed, and its use in the assessment of vascular and aneurysm disease has been recommended [188,207].

The self-administered United Kingdom version of the SF-36 was sent to all patients 6-months after aneurysm repair. This time point was chosen as representing the time by which patients undergoing elective AAA repair regain their preoperative levels of HRQoL [188]. Repeat questionnaires were sent after 2-weeks if no reply was received. Questionnaires were scored according to the methodology described by Ware and colleagues [248]. Mean scores and standard deviations were calculated for each group and compared. Further comparison was made between the age and sex-matched general population data for the United Kingdom [249].

Statistical analysis was performed using SPSS for Windows Release 11.0.0 (SPSS Inc., Chicago, Illinois, USA). Between groups differences were determined by the unpaired *t*-test or Mann-Whitney *U* test for parametric and non-parametric continuous variables respectively; $P \leq 0.05$ was considered significant.

7.3. Results

Seventy-three consecutive patients were admitted with a ruptured AAA during the study period, of whom 57 (78%) underwent attempted aneurysm repair. Reasons for non-operative management are listed in Table 7.1. Of these 57, 30 (53%) survived to discharge from hospital and were included in this study. There were 26 men and four women of median (range) age 68 (53-85) years. Twenty-two of the 30 patients had haemodynamic instability, as defined by a preoperative blood pressure of <90mmHg, before operation. During the same period, 78 patients underwent elective repair of an asymptomatic aneurysm and 19 underwent urgent repair of an acutely symptomatic aneurysm. Thirty patients with asymptomatic AAA were selected as suitable age and sex-matched controls. The median (range) age of the 26 male and four female control patients was 70 (59-83) years (P=.440). Patients who had repair of a ruptured aneurysm had a median (range) hospital stay of 14 (7-59) days, while patients undergoing elective operation stayed for a median (range) of 11 (7-37) days (P=.048). Median (range) SAP II score for patients undergoing ruptured AAA repair was 30 (18-52) and for patients who had elective repair it was 16 (12-30) (P<.001).

At 6-month follow-up, all patients in both the study and control groups were still alive. Twenty-eight of the 30 patients who survived ruptured aneurysm repair had been discharged to their homes, while one patient required nursing home care and one remained in a geriatric rehabilitation unit. All patients in the control group were discharged home. The SF-36 questionnaire was self-administered by all but one patient who required the aid of a proxy. All patients from both groups returned a completed form.

Comparison of SF-36 scores of the ruptured AAA, elective AAA and normal populations are shown in Tables 7.2-4. There was no statistically significant difference between patients who had undergone ruptured aneurysm repair or an elective aneurysm repair in any of the health domains. However, when HRQoL in survivors of aneurysm rupture was compared to that of the matched normal population, the former group had significantly worse outcomes in terms of role limitations due to physical and emotional problems were apparent. There were no statistically significant differences in the other six health domains. In contrast, comparison of functional outcome between patients who underwent elective repair and the normal population showed the former group to have significantly worse outcomes in the domains of physical function, bodily pain and social functioning, as well as role limitations due to physical and emotional problems.

Table 7.1. Primary reason for refusal of surgery in 16 patients.

Reason for refusal	Number of patients
Cardiac arrest / Refractory LOC	7
Age related comorbidity	5
Cardiorespiratory comorbidity	2
Malignancy	1
Dementia	1

LOC – Loss of consciousness

Table 7.2. Mean (SD) SF-36 scores in 30 patients after ruptured AAA repair and 30 patients after elective AAA repair

Health domain	Ruptured AAA repair	Elective AAA repair	P value
Physical function	65 (27)	55 (30)	0.222
Role limitations physical	58 (29)	57 (33)	0.855
Bodily pain	69 (28)	60 (28)	0.196
General health	62 (24)	63 (22)	0.770
Vitality	55 (23)	54 (24)	0.911
Social functioning	78 (32)	71 (31)	0.441
Role limitations emotional	68 (33)	71 (35)	0.733
Mental health	77 (19)	76 (17)	0.782
Mental summary score	49 (12)	49 (12)	0.842
Physical summary score	44 (11)	40 (11)	0.297

Table 7.3. Mean (SD) SF-36 scores in 30 patients after ruptured AAA repair and the age and sex-matched normal population

Health domain	Ruptured AAA repair	Normal population	P value
Physical function	65 (27)	72 (9)	0.162
Role limitations physical	**58 (29)**	**72 (5)**	**0.016**
Bodily pain	69 (28)	77 (3)	0.167
General health	62 (24)	64 (2)	0.638
Vitality	55 (23)	62 (4)	0.116
Social functioning	78 (32)	83 (4)	0.339
Role limitations emotional	**68 (33)**	**87 (4)**	**0.004**
Mental health	77 (19)	79 (2)	0.521

Table 7.4. Mean (SD) SF-36 scores in 30 patients after elective AAA repair and the age and sex-matched normal population

Health domain	Elective AAA repair	Normal population	P value
Physical function	**55 (30)**	**72 (9)**	**0.007**
Role limitations physical	**57 (33)**	**72 (5)**	**0.019**
Bodily pain	**60 (28)**	**77 (3)**	**0.003**
General health	63 (22)	64 (2)	0.926
Vitality	54 (24)	62 (4)	0.098
Social functioning	**71 (31)**	**83 (4)**	**0.043**
Role limitations emotional	**71 (35)**	**87 (4)**	**0.018**
Mental health	76 (17)	79 (2)	0.253

7.4. Discussion

Postoperative quality of life is a frequently neglected outcome measure in the assessment of surgical interventions. In contrast, oncological interventions have been routinely subjected to HRQoL analysis and the UK Medical Research Council has introduced HRQoL measures in their guidelines for clinical trials [250,251]. Ruptured AAA repair, and subsequent recuperation, is associated with a major physical and psychological insult. Nevertheless, there are few data on functional outcomes in this situation. The present series contains the first prospective data examining HRQoL outcomes following ruptured aneurysm repair. While the limitations of the data are acknowledged in as much as preoperative assessment of HRQoL is absent and the sample size is relatively small, the nature of ruptured AAA does not allow the former and only three retrospective series have individually reported more patients [196,197,203]. Multivariate analysis on current data to identify independent predictors of functional outcome has not been carried out as the small sample size renders such analysis vulnerable to statistical error.

Present data show that the quality of life of survivors of ruptured AAA is no different from that of patients who have undergone elective aneurysm repair. Furthermore, this recovery in functional performance is apparent within 6-months of operation. It is interesting that functional recovery is so similar between two groups that are clearly different in terms of illness severity and hospital stay. The 30 patients with ruptured aneurysm are a highly selected group who have survived to reach hospital, have been selected for operative intervention, survived operation, and survived to 6-month follow-up. Survival after aneurysm rupture is influenced by good preoperative

physiological status, and this may predispose these patients to achieving good functional outcomes [113]. Existing studies of HRQoL after elective open repair of AAA have shown that patients regain their preoperative functional status within 3 to 6-months of operation [188,252]. It would appear, from the present data, that recovery of HRQoL after ruptured aneurysm repair follows a similar time course. However, if HRQoL assessment had been performed at an earlier time point from operation, differences in functional outcome may have been apparent.

Eight previously published series compare HRQoL outcome after ruptured and elective AAA repair [193,194,196-8,200,205,206]. All are retrospective and have a varying duration of follow-up rendering them vulnerable to an even greater selection bias. In contrast, the present prospective data describe a consecutive series of patients with ruptured AAA with a fixed follow-up interval. All but one of the preceding retrospective studies have concluded that ruptured aneurysm survivors regain a quality of life similar to that of patients undergoing elective AAA repair. Magee and colleagues are the only authors to have demonstrated a significant deterioration in functional outcome following ruptured AAA repair compared to elective repair [197]. They reported a fall from near perfect HRQoL to considerable disability after ruptured aneurysm repair. However, in their series patients who underwent elective repair were not matched for age, and, in fact, were much younger than the patients with ruptured AAA. It is noteworthy that there is relative consistency in SF-36 health domain scores between the present data and the three other studies that have used this instrument [199,201,202]. Such a finding across different series supports the conclusion that survivors of ruptured AAA do regain a good quality of life. Though a

selective policy of operative intervention has governed this series, the good functional outcomes attained do justify an aggressive policy of surgical intervention for ruptured aneurysm.

The present series shows that survivors of ruptured aneurysm have poorer outcomes in terms of role limitations due to physical and emotional problems when compared to the general population. It is, perhaps, unsurprising that they have some functional disability after such major surgical intervention. However, no other differences were demonstrated in the other health domains. It is interesting to note that functional outcome after elective aneurysm repair displayed poorer outcomes in more health domains – physical functioning, bodily pain and social functioning. Taking these results at face value, one would infer that patients who survived ruptured aneurysm repair had a better functional outcome than those who had an elective operation. This, clearly, is counterintuitive. It is likely that this discrepancy is related to the selection of biologically robust individuals for emergency operation and that they survive to have a good functional recovery after surgery. A possible alternative is that a near-death experience has a positive impact on an individual's perception of his or her functional performance, resulting in a higher rating of HRQoL.

This study provides benchmark HRQoL data for patients who survive open repair of ruptured AAA. In the future, functional outcomes after endovascular repair of intact or ruptured aneurysm can be assessed against these results.

8. Conclusions

8.1. Summary

Twenty years of preceding clinical research have failed to clarify whether outcome in patients with ruptured AAA can be accurately predicted in the preoperative period. Furthermore, patient selection for attempted operative repair may have been justified on the basis of unsound risk scoring instruments. The aims of the present thesis were to document contemporary outcomes and examine risk factors thought to relate to poor outcome in patients with ruptured AAA, to validate existing scoring systems and to demonstrate whether the prediction of death after aneurysm rupture is feasible.

The Hardman Index and Glasgow Aneurysm Score are well cited scoring instruments that have been recommended as predictive scoring tools for patients with ruptured AAA. In particular, the Hardman Index has been validated by a number of retrospective series-it was proposed that the instrument could accurately identify patients who would not survive any attempt at operative intervention. However, data from this thesis question the validity and accuracy of these instruments as both predictive tools and risk-scoring instrument for comparative audit for the first time. These findings have now been supported by retrospective data from other centres. It now appears to be indisputable that the Hardman Index is an imprecise tool for the prediction of outcome after aneurysm rupture. Most importantly, the model does not allow the identification of any patients in whom attempted AAA repair is futile. The Glasgow Aneurysm score demonstrated poor validity when applied to retrospective and prospective data from this centre. In contrast, other centres have reported good validity and predictive ability for this tool. It remains unclear whether the Glasgow score is of clinical use but further study is needed.

POSSUM methodology was never designed for use as a tool to predict outcome. Rather, its use was confined to risk stratification of patients to support comparative audit. However, the preoperative (physiology score only) risk equations that have been derived for application in arterial surgery (V-POSSUM) and, specifically, ruptured aneurysm (RAAA-POSSUM) performed poorly when applied to the current series. The RAAA-POSSUM demonstrated a significant lack of fit when applied and the V-POSSUM equation tended towards lack of fit and seemed to underpredict mortality at the lowest bands of risk. Whether this lack of fit is confined to the preoperative model only is unclear. Nevertheless, these are the first data to question the performance of the RAAA-POSSUM model, though the validity of the V-POSSUM equation has been reported to underperform in a selected group of patients with ruptured AAA before.

In an attempt to develop a model for predicting outcome after AAA rupture, preoperative variables from both a retrospective and prospective dataset were analysed. On multivariate logistic regression analysis, no variable retains independent statistical significance. However, certain variables were significant on univariate analysis and tended towards significance on multivariate analysis. In particular, these included the triad of preoperative haemoglobin concentration <9g/dl, best in-hospital Glasgow Coma Scale <15 and a systolic blood pressure of <90mmHg. When compiled to form a cumulative risk score with equal weighting, these variables demonstrated good predictive power. The accumulated score can be translated to one of three bands of mortality risk-low (<30%), medium (~50%) and

high (~80%). When prospectively validated on our own data, the model performed well and retained a high level of statistical significance. This novel risk scoring instrument appeared to have better validity and easier applicability than existing models. It now requires external validation to confirm its performance.

The fact that the present data stemmed from a high volume tertiary centre may account for the lack of fit of pre-existing scoring systems. The majority of existing analyses have come from centres that do not have a high volume experience in the management of ruptured AAA. As a result, our risk modelling was unique and highly specific towards our data. If applied to data from other centres, it may not demonstrate the same good fit. However, there is an increasing drive, in the UK, towards the centralisation of emergency vascular services in high volume centres. It might be anticipated that our risk model will continue to perform well in such units.

The primary aim of this thesis was to develop a method of accurately identifying patients who are unsalvageable despite attempted operation for ruptured AAA. Analysis of the data has failed to demonstrate a robust and reproducible method of achieving this aim. Even extreme preoperative variables, such as unconsciousness and cardiac arrest, have been confirmed as not being uniformly fatal. It may be concluded patients in whom surgical intervention would be futile are impossible to identify preoperatively. Therefore, where a selective policy of operative intervention is utilised, each case must be taken on its own individuals merits. Although attributing patients to the highest level of risk, using our novel prognostic index, will

help to objectively justify non-operative management, experienced clinical judgement will have to remain at the forefront of any decision making.

Cardiac troponins have revolutionised the diagnosis and management of myocardial injury. Previously undetectable myocardial injury is now quantifiable and permits earlier intervention when indicated. From the current series, it is noted that about half of all patients who survive initial repair of ruptured AAA will suffer a detectable myocardial injury. Around half of these will be clinically silent. Interestingly, even a minor elevation in cardiac troponin in the early perioperative period confers an increased risk of postoperative death, and is associated with a prolonged stay on the intensive care unit. It is acknowledged that a number of non-cardiac causes, found in patients with ruptured AAA, may cause an elevation of cardiac troponin. The early elevations seen in the present data (within 24hrs) suggest that it is a primary cardiac injury that is responsible for the elevation in troponin and the attendant increase in mortality and morbidity. The practical application of such a finding is less obvious. Once elevated cardiac troponins have been detected, there are limited opportunities for remedial intervention. However, it may be that more aggressive cardiorespiratory support or pharmacological intervention to optimise cardiac function may improve outcome in this subgroup of patients. Alternatively, it identifies a group of patients who are at increased risk of postoperative complication and may help rationalise treatment. Further work is needed to investigate both these issues and the impact of raised perioperative troponins in the longer term. Existing data have shown that elevation of cardiac troponins confers prognostic information, in terms of survival, beyond one year [229]. Alternatively, the interplay between myocardial injury and the

systemic inflammatory response that is evoked postoperatively in patients with ruptured aneurysms needs more consideration.

C-reactive protein (CRP) has been reported to be an accurate predictor of outcome in an array of clinical situations. These include acute coronary syndrome, cancer and the critically ill on intensive care units. Whether CRP has prognostic value in acute AAA patients remains uncertain. From the current data, it is apparent that there is an upregulation of the systemic inflammatory response, as measured by CRP, in patients with acutely symptomatic and ruptured AAA. However, the present study has been unable to relate this upregulation to outcome, as assessed by mortality. The presence of a systemic inflammatory response is likely to influence clinical outcome. It may be that a larger study based on these pilot data will be able to demonstrate the impact of raised CRP on survival. Further investigation may also examine the prognostic value of the newer high-sensitivity CRP assays. CRP remains a novel potential prognostic biomarker in patients with acute aneurysmal disease.

Outcome after aneurysm rupture has always been largely considered in the black and white terms of survival or death. Interest in perioperative morbidity does exist but is less well described in the literature. This was the first prospective study of functional outcome in survivors of ruptured AAA. Interestingly, despite the greater severity of illness encountered in patients undergoing emergency AAA repair, they achieve a similar functional outcome to age and sex-matched patients undergoing elective aneurysm repair within 6-months. Furthermore, when compared to the age-matched general population, survivors of aneurysm rupture achieve similar functional

outcomes. These data support an aggressive policy of management for patients with ruptured AAA. Though it is not possible to predict which patients will obtain the best functional recovery, the majority of those who survive regain an acceptable quality of life.

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Appendix

Hardman Index Variables

- Haemoglobin of less than 9g/l,
- Creatinine of more than 190umol/l,
- Electrocardiographic ischaemia,
- In-hospital loss of consciousness
- Age greater than 76 years

The presence of 3 or more variables is reported to be uniformly fatal [111].

Glasgow Aneurysm Score

Risk score = (age in years)+(17 for shock)+(7 for myocardial disease)+(10 for cerebrovascular disease)+(14 for renal disease).

Myocardial disease - documented myocardial infarction and/or on-going angina.

Cerebrovascular disease - all grade of stroke including transient ischaemic attacks.

Renal disease - history of chronic or acute renal failure and/or urea greater than 20mmol/l and/or creatinine over 150μmol/l at presentation [115].

POSSUM physiological and operative variables

Physiological	Operative
Age (years)	Operation category (minor, intermediate, major, major+)
Cardiac signs	No. of procedures
Respiratory signs	Total blood loss (ml)
Systolic blood pressure (mmHg)	Peritoneal soiling
Pulse rate (per min)	Malignancy
Glasgow Coma Score	Timing of operation
Serum urea (mmol/l)	
Serum sodium (mmol/l)	
Serum potassium (mmol/l)	
Haemoglobin (g/l)	
White cell count ($\times 10^9$/l)	
Electrocardiogram	

Mortality Risk equations (R is the risk of mortality):

POSSUM: ln (R/1-R) = -7.04 + (0.13 x physiological score) + (0.16 x operative severity score)

V -POSSUM: ln (R/1-R) = -8.0616 + (0.1552 x physiological score) + (0.1238 x operative severity score)

V –POSSUM (Physiology score only): ln (R/1-R) = -6.0386 + (0.1539 x physiological score)

RAAA -POSSUM: ln (R/1-R) = -4.9795 + (0.0913 x physiological score) + (0.0958 x operative severity score)

RAA –POSSUM (Physiology score only): ln (R/1-R) = -2.7569 + (0.0968 x physiological score) [118, 123,124]

Vancouver Scoring System

Variable	Category	Coefficient (Constant=-3.41)
Age		0.062 x age
Loss of consicousness	Yes	1.14
	No	-1.14
Cardiac arrest	Yes	0.60
	No	-0.60

Probability of death= e^x / 1 + e^x, where e is the base of the natural logarithm and x is the constant (-3.44) + sum of coefficients for the significant variables [102].

Edinburgh Ruptured Aneursym Score

- Haemoglobin of less than 9g/dl,
- Glasgow Coma Scale <15 in-hospital,
- Systolic blood pressure <90mmHg in-hospital

Publications

Publications arising from this thesis:

1. Quality of life after ruptured abdominal aortic aneurysm repair. A.L. Tambyraja, S.C.A. Fraser, J.A. Murie, R.T.A. Chalmers. *European Journal of Vascular & Endovascular Surgery* 2004; 28: 229-233
2. Validity of the Glasgow Aneurysm Score and Hardman Index in predicting outcome after ruptured abdominal aortic aneurysm repair. A.L. Tambyraja, S.C.A. Fraser, J.A. Murie, R.T.A. Chalmers. *British Journal Surgery* 2005; 92: 570-573
3. Cardiac troponin I predicts outcome after ruptured abdominal aortic aneurysm repair. A.L. Tambyraja, A.R.W. Dawson, J.A. Murie, R.T.A. Chalmers.*British Journal of Surgery* 2005; 92: 824-827
4. Functional outcome after open repair of ruptured abdominal aortic aneurysm. A.L. Tambyraja, S.C.A. Fraser, J.A. Murie, R.T.A. Chalmers. *Journal of Vascular Surgery* 2005; 41: 758-761
5. Systemic inflammation and repair of abdominal aortic aneurysm. A.L. Tambyraja, A.R.W. Dawson, D. Valenti, J.A. Murie, R.T.A. Chalmers. *World Journal of Surgery* 2007; 31: 1212-1216
6. Predictors of outcome after abdominal aortic aneurysm rupture - The Edinburgh Ruptured Aneurysm Score. A.L. Tambyraja, J.A. Murie, R.T.A. Chalmers. *World Journal of Surgery* 2007; 31: 2243-2247
7. Prediction of outcome after abdominal aortic aneurysm rupture-A systematic review. A.L. Tambyraja, J.A. Murie, R.T.A. Chalmers. *Journal of Vascular Surgery* – 2008; 47: 222-230

8. Prediction of outcome after abdominal aortic aneurysm rupture-A prospective evaluation. A.L. Tambyraja, A.J. Lee, J.A. Murie, R.T.A. Chalmers. *Journal of Vascular Surgery* 2008; 47: 282-286

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REVIEW

Quality of Life After Repair of Ruptured Abdominal Aortic Aneurysm

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Background. *Ruptured abdominal aortic aneurysm (AAA) continues to be associated with high operative mortality. Though survivors can expect to return to a normal life expectancy, their postoperative health related quality of life (HRQoL) remains uncertain. This review examines HRQoL following operative repair of ruptured AAA.*
Methods. *PreMedline, Medline and Embase databases were searched for clinical studies relating to quality of life following repair of ruptured AAA. Reference lists of relevant papers were also reviewed.*
Results. *Fourteen retrospective-observational studies of postoperative quality of life following repair of ruptured AAA were identified. Both validated and non-validated tools for generic HRQoL assessment were used. All but one study showed no significant difference in overall HRQoL following ruptured AAA repair when compared to both the normal age-adjusted population and patients undergoing elective repair of intact AAA. However, survivors of ruptured AAA did exhibit significant reductions in the isolated domains of physical function, social behaviour and general well-being.*
Conclusions. *There are few studies of HRQoL following repair of ruptured AAA. These reports are retrospective, have small sample sizes and use generic instruments for HRQoL assessment. The findings suggest that survivors of ruptured AAA may attain a similar functional outcome to patients undergoing elective AAA repair and the age-matched healthy population. However, these results must be interpreted with caution and further prospective study is required.*

Key Words: Quality of life; Abdominal aortic aneurysm; Functional outcome.

Introduction

e traditional measures of surgical outcome have en in terms of perioperative morbidity and mor-ity. However, the importance of health-related ality of life (HRQoL) in the assessment of outcome s gained increased recognition. The rationalisation health care finances has motivated the need to antify outcomes of medical interventions and in the aluation of cost, quality of life issues must be nsidered.

The prevalence of abdominal aortic aneurysm AA) is increasing in the United Kingdom and rently accounts for approximately 8000 deaths per num.[1] The efficacy and durability of elective AAA pair in terms of perioperative morbidity and rtality, long-term survival, quality of life and cost-ectiveness are well established.[2–4] However, despite advances in perioperative care, repair of ruptured AAA continues to be associated with an operative mortality rate of 45% and high attendant financial cost and resource utilisation.[5,6] Though survivors are reported to attain the same rates of survival as the normal population, functional outcome in terms of HRQoL is uncertain.[7] Such data are essential to quantify the efficacy of current intervention for ruptured AAA.

Method

The Medline and PreMedline (January 1966 to July 2003) and Embase (January 1980 to July 2003) electronic databases were searched. The Ovid search engine (version 16.2.0; Ovid Technologies, New York, USA) was employed. The search strategy used the keywords 'quality of life' and 'aneurysm', with the Boolean operator 'and'. Criteria for inclusion were studies assessing postoperative quality of life in

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tients undergoing operative repair of ruptured AA. Manual searching of reference lists from articles rieved by electronic searching was also used. ticles retrieved were restricted to those published English. All identified articles were obtained rough local library collections and The British brary.

Results

urteen studies investigating quality of life in ients who had survived operative repair of rup-ed AAA were identified from computerized and nual searches.[7–20] (Table 1). Three articles from the ginal searches were excluded, as they did not lertake quantitative HRQoL assessment.[18–20]

Of the 11 remaining papers, all were retrospective-ervational studies. Publications dates ranged from 6 to 2003, with study periods ranging from 1962 to 3. Three papers reported quality of life specifically selected groups of patients (octogenarians) but are luded in the present review.[8,9,12] Two studies mbined patients with symptomatic, intact AAA dergoing emergency repair with patients with ptured AAA.[12,15] Three studies used non-validated struments to assess quality of life while eight articles ed validated, generic HRQoL instruments.

Non-validated health related quality of life assessment

these three studies, all utilised self designed estionnaires to assess quality of life.[8,9,12] The mid-ne point of all three reports was earlier than 1985. vo studies on survivors of ruptured AAA concluded at preoperative physical status was regained in the ajority of patients within one-year.[8,9] The remaining udy analysed functional outcome in patients aged er 80 years who had survived emergency repair of th intact and ruptured AAA.[12] Though it is ncluded that octogenarians surviving emergency AA surgery enjoy a reasonable quality of life, specific itcomes of patients undergoing ruptured AAA rgery are not extractable.

Validated health related quality of life assessment

ght studies used validated instruments for HRQoL sessment. Rohrer and van Ramshorst applied odified versions of the Self-evaluation of function ale to their cohorts of ruptured AAA survivors.[7,10] ese reports used patients who had undergone ective AAA repair as controls. Both series failed to demonstrate differences in overall HRQoL between the ruptured and elective AAA groups. However, Rohrer reported a statistically significant reduction in the domain of general sense of well-being amongst patients with ruptured AAA. Similarly, van Ramshorst noted that patients undergoing elective AAA repair tended to be significantly more active in the domain of social behaviour than their counterparts with ruptured lesions.

Magee and co-workers used the York quality of life questionnaire with Rosser index classification on patients who underwent ruptured AAA repair and their counterparts undergoing elective repair.[11] Patients undergoing elective repair were noted to have improved HRQoL scores after operation while those undergoing emergency repair reported a diminished quality of life.

Hennessy studied patients who survived ruptured AAA repair compared to matched patients undergoing elective repair.[14] It is unclear whether this patient cohort represents a selected group of patients surviving ruptured AAA repair or a consecutive series. No significant differences, in terms of HRQoL, were elicited.

Four studies, reported between 1998 and 2003, used the generic Medical Outcomes Study Short Form 36 (SF36), or its derivative the RAND 36-Item Health Survey (RAND36), to assess quality of life.[13,15–17] These instruments comprise 36 questions covering eight health domains.

Joseph and colleagues studied SF36 results from survivors of ruptured AAA compared to age-matched healthy controls.[16] The majority of patients were reported to have the same quality of life compared to controls. No significant differences or trends between groups, in terms of physical functioning, were identified.

Eskandari's and Bohmer's comparisons of survivors of ruptured AAA and the age-matched general population also revealed no significant differences in SF 36 scores between the two groups.[13,15] However, survivors of ruptured AAA trended towards lower functional outcome scores in six of the eight domains, including those of physical function, in Eskandari's report and lower physical function scores in Bohmer's series.

In the largest study to date, Korhonen and colleagues administered the RAND36 questionnaire to 82 survivors of ruptured AAA compared to the age and sex-matched general population.[17] Again, significant differences in physical functioning were demonstrated between ruptured AAA patients and their healthy counterparts. No other differences, in terms of

Table 1. Studies quoting quality of life after ruptured abdominal aortic aneurysm repair in chronological order according to year of publication

Reference	Year of publication	Study design	Age range (years)	Number of patients	HRQoL instrument	Follow-up period (months)	Control group	Results
O'Donnell *et al.*[8]	1976	Retrospective	≧ 80	5	Authors design	Unknown	Elective AAA repair Non-operatively treated AAA Expanding AAA	Regained or improved physical status
Treiman *et al.*[9]	1982	Retrospective	≧ 80	7	Authors design	48–156	None	Regained physical status at six-months
Rohrer *et al.*[7]	1988	Retrospective	59–84	26	Adapted from Self evaluation of life function scale	Unknown	Elective AAA repair	No difference in physical independence, psychological well-being and social interaction. Reduced sense of general well being after RAAA
Van Ramshorst *et al.*[10]	1990	Retrospective	Unknown	55	Adapted from Self evaluation of life function scale and psychosocial adjustment to illness scale	20–57	Age and sex-matched elective AAA repair	No difference apart from reduced level of social behaviour
Magee *et al.*[11]	1992	Retrospective	Unknown	45	York QoL questionnaire and Rosser index	18–42	Elective AAA repair	Deterioration in HRQoL
Currie *et al.*[18]	1992	Retrospective	≥80	9*	Authors design	Unknown	Elective AAA repair Age and sex matched normal population	No differences
Gefke *et al.*[18]	1994	Retrospective	Unknown	41*	Authors design	Unknown	None	Unknown
Moriyama *et al.*[20]	1994	Retrospective	71†	32	Unknown	5–101	Elective AAA repair	Unknown
Matsushita *et al.*[19]	1997	Retrospective	Unknown	≤17	Authors design	49†	Elective AAA repair	Unknown
Hennessy *et al.*[14]	1998	Retrospective	54–81	14	Hopkins symptom checklist, general Health questionnaire and Rosser index	4–29	Age and sex-matched elective AAA repair	No differences
Eskandari *et al.*[13]	1998	Retrospective	70†	15	SF-36	9–48	Age-matched normal population	No differences
Bohmer *et al.*[15]	1999	Retrospective	54–85	28*	SF-36	12–156	Age-matched normal population	No differences
Joseph *et al.*[16]	2002	Retrospective	60–81	26	SF-36	Unknown	Age-matched normal population	No difference/better HRQoL
Korhonen *et al.*[17]	2003	Retrospective	47–96	82	RAND-36	10–69	Age and sex-matched normal population	No difference apart from reduced physical function

HRQoL, health related quality of life.
*Includes patients undergoing emergency repair of symptomatic intact abdominal aortic aneurysm.
†Mean age.

RQoL, were identified between the study and ontrol populations.

Discussion

espite an increase in the number of elective AAA pairs performed, an associated decline in the idence of ruptured AAA has not been borne out.[21] rthermore, recent advances in perioperative care ve failed to make a significant impact on survival llowing operative repair of ruptured aneurysm and rtality remains around 40%.[5] Within the constraints finite health care resource, there is a need to assess l compare the outcomes of medical interventions. aluation of a clinical intervention must not only take o account the traditional primary outcomes of ath, disability or cure but also the patient's rspective of outcome. To assess the benefit of an tervention, evidence for the impact on the patient in ms of health status and HRQoL is essential.[22]

Of the 11 studies presently reviewed, all have fficiencies in their design. The small number of udies, sample sizes, methodology and variation in llow-up period do not permit meaningful meta-alysis and render direct comparison awkward. In rticular, studies that utilised non-validated HRQoL struments and those that amalgamate data from tients with intact and ruptured AAA must be terpreted with caution. Furthermore, all series ere retrospective in design and are susceptible to as. With the progress of time following ruptured AA repair, patients become increasingly selected in at they have survived to reach hospital, survived perative repair, survived their postoperative recovery nd agreed to HRQoL assessment. It may be argued at this process specifically selects patients who are iologically more robust and predisposed to achieve ood functional outcomes. Similarly, some patients ith ruptured AAA will have been deemed unfit for ective repair and again are less likely to attain good nctional recovery when compared to patients under-oing elective repair.

Of the seven studies that used validated HRQoL struments and failed to establish a difference in RQoL after ruptured AAA repair, all used generic RQoL instruments. In particular, the reliability, lidity and consistency of the SF36, and its derivative e RAND 36, have been confirmed. The SF36 is the ost widely used quality of life instrument in the edical literature and its use, in the assessment of scular disease, has been previously recommended.[23]

Generic tools require large sample sizes to demon-rate statistically significant HRQoL differences, due to the large standard deviations of health profiles.[24] Of the four articles that used the SF36 or RAND 36 instruments, only one study included more than 30 patients. Interestingly, this report on 82 patients by Korhonen was the only one to detect significant reductions, in the isolated domain of physical functioning, amongst ruptured AAA survivors.

Overall perception of HRQoL, in the three studies that utilised generic instruments other than the SF36 or RAND 36, was not significantly different between patients undergoing emergency or elective AAA repair. However, the absence of differences may be attributable to small sample sizes and use of a generic HRQoL tool. It is noteworthy that significant reductions in the domains of general well-being and social behaviour were detected amongst ruptured AAA survivors.

Magee and colleagues demonstrated a significant deterioration in functional outcome following ruptured AAA repair when compared to elective repair. They noted a fall in HRQoL from near perfect health preoperatively to considerable disability at postoperative follow-up. Such a conclusive finding has not been reproduced in any other series reporting on ruptured AAA survivors. However, prospective studies in patients surviving intensive care admission have described similar reductions in HRQoL.[25,26] If such a finding were true for survivors of ruptured AAA repair, arguments for aneurysm screening and elective repair would be further supported.

In the United Kingdom, the financial cost of ruptured AAA repair has been reported to be almost double that of elective repair.[27] Nevertheless, cost-analyses of surgical repair of ruptured AAA have shown that surgical treatment remains a cost-effective intervention.[28] The attainment of normal life expectancy after successful repair of ruptured AAA versus the alternative of immediate death is the predominant reason for such a finding. However, these analyses fail to consider outcome in terms of HRQoL and functional outcome following repair of ruptured AAA remains largely uncertain. If survivors of ruptured AAA were returned to a significant level of functional disability despite a near-normal life expectancy, the efficacy of intervention becomes less apparent. Indeed, an intervention that encompasses a postoperative quality of life that will be unacceptable to the patient may even be regarded as futile.[29] This concept has important implications where a selective policy in the management of ruptured AAA is employed; it might be argued that quality-adjusted survival rather than absolute survival should be used to guide operative selection.[14] With the introduction of endovascular repair for ruptured AAA, any comparison of outcome

th conventional repair should also consider post-erative functional status.

The limited current evidence suggests that the ajority of survivors of RAAA may expect to regain eir preoperative quality of life. However, a pro-rtion will experience postoperative deterioration of ir functional status. No existing reports inform ether postoperative functional outcome can be related to preoperative risk factors. Further pros-tive studies are needed to clarify the HRQoL comes of survivors of ruptured AAA repair.

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Original article

Validity of the Glasgow Aneurysm Score and the Hardman Index in predicting outcome after ruptured abdominal aortic aneurysm repair

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Background: The Glasgow Aneurysm Score and the Hardman Index have been recommended as predictors of outcome after repair of ruptured abdominal aortic aneurysm (AAA). This study aimed to assess their validities.

Methods: Patients admitted to a single unit with a ruptured AAA over a 2-year interval (2000–2001) were identified from a prospectively compiled database. Hospital records of all patients undergoing attempted operative repair were reviewed. The Glasgow Aneurysm Score and the Hardman Index were calculated retrospectively and related to clinical outcome.

Results: One hundred patients were admitted with a ruptured AAA. Of these, 82 underwent attempted operative repair and were included in the study: 68 men and 14 women, of median age 73 (range 54–87) years. Thirty (37 per cent) patients died after the operation. The Glasgow Aneurysm Score was a poor predictor of postoperative mortality. The area under the Receiver–Operator Characteristic curve was 0·606 ($P = 0·112$, 95 per cent c.i. 0·483–0·729). Similarly, the Hardman Index failed to predict postoperative mortality accurately ($P = 0·211$, χ^2 for trend). Of nine patients in this series with three or more Hardman criteria, generally held to be fatal, six survived.

Conclusion: Contrary to previous reports, The Glasgow Aneurysm Score and the Hardman Index were poor predictors of postoperative mortality after repair of a ruptured AAA in this study.

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Introduction

The incidence of abdominal aortic aneurysm (AAA) is increasing in the UK and at present AAA accounts for approximately 8000 deaths each year[1]. Despite advances in perioperative care, outcome after ruptured AAA repair has remained relatively unchanged over the past 40 years, with an operative mortality rate in excess of 40 per cent[2].

It has been suggested that the outcome after open repair of a ruptured AAA could be improved by operating on patients with a reasonable operative risk. Similarly, it may be futile or even unethical to perform surgery or to continue treatment in patients with prohibitive risk.

However, no robustly validated methods exist by which to identify patients unlikely to survive emergency aneurysm repair and selection is frequently subjective.

The Glasgow Aneurysm Score (GAS) and the Hardman Index are two practical, objective, predictive scoring systems recommended for use in patients with a ruptured AAA[3,4]. This study aimed to assess their validity in a series of patients from a high-volume centre.

Patients and methods

All patients admitted to the Edinburgh Vascular Surgical Service with a ruptured AAA over a 2-year interval (January 2000 to December 2001) were identified from a prospective database and included in a retrospective observational study. The database, together with hospital records, provided demographic details as well as clinical and operative information for all patients undergoing

attempted repair of a ruptured AAA. Operation was defined as the delivery of an anaesthetic with the intention of performing AAA repair. Ruptured aneurysm was defined as the presence of retroperitoneal or intraperitoneal blood or both from an aortic aneurysm. All patients were operated on by one of six consultant vascular surgeons. The GAS and the Hardman Index were recorded for each patient and related to subsequent clinical outcome.

The GAS was calculated using the following formula: risk score = age in years + 17 for shock + 7 for myocardial disease + 10 for cerebrovascular disease + 14 for renal disease[3]. Shock was defined on clinical grounds by tachycardia, hypotension, pallor and sweating. Myocardial disease was previously documented myocardial infarction, ongoing angina or both. Cerebrovascular disease referred to all grades of stroke including transient ischaemic attacks. Renal disease was one or more of a history of chronic or acute renal failure, urea over 20 mmol/l or creatinine over 150 μmol/l at presentation[3]. A score of more than 95 is reported to correlate with a mortality rate of 80 per cent[5].

The Hardman Index was derived from five preoperative variables: age greater than 76 years, serum creatinine over 190 μmol/l, haemoglobin less than 9 g/dl, myocardial ischaemia on electrocardiogram and a history of loss of consciousness after arrival in hospital[6]. A patient may score between 0 (no Hardman variables present) and 5 (five Hardman variables present). It has been reported that the presence of three or more variables is uniformly fatal[7].

Statistical analysis was performed using SPSS for Windows Release 11.0.0 (SPSS Inc., Chicago, Illinois, USA). The Receiver–Operator Characteristic (ROC) curve and χ^2 test for trend was used to evaluate the performance of the GAS and the Hardman Index respectively in predicting postoperative death. Differences between groups for non-parametric continuous variables were determined by the Mann–Whitney U test; $P \leq 0{\cdot}05$ was considered significant.

Results

One hundred patients were admitted with a ruptured AAA during the study interval. Of these, 18 were deemed unfit for aneurysm repair owing to prohibitive co-morbidity: 11 men and seven women of median age 81 (range 66–97) years. Eight patients had previously been assessed and deemed unsuitable for elective repair. The primary reasons for non-operative management in the remainder were cardiorespiratory co-morbidity (seven), cardiac arrest (three), malignancy (three) age-related co-morbidity (three) and dementia (one). The median GAS in patients who did not undergo operation was 102 (range 84–127). These patients, in general, were not subject to a full remit of baseline investigations on admission to allow accurate Hardman Index scoring.

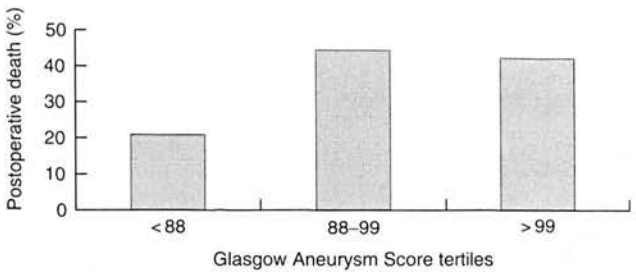

Fig. 1 Postoperative mortality rates for three tertiles of the Glasgow Aneurysm Score

The remaining 82 patients underwent attempted repair of a ruptured AAA and were included in the present analysis: 68 men and 14 women of median age 73 (range 54–87) years. Thirty (37 per cent) patients died after operation. Of all patients admitted to hospital with a ruptured AAA during the study interval, 48 (48 per cent) died.

Glasgow Aneurysm Score

The GAS was a poor predictor of mortality after ruptured AAA repair. The mortality rates in terms of tertiles of GAS distribution are shown in *Fig. 1*. The median (range) GAS was not significantly different in patients who survived operative repair and those who did not: 93 (57–125) *versus* 96 (71–115) ($P = 0{\cdot}112$). Analysis of the ROC curve showed that the GAS had an area under the curve of 0·606 (95 per cent c.i. 0·483–0·729; s.e. 0·063; $P = 0{\cdot}112$) for predicting postoperative death.

Hardman Index

There was no significant association between Hardman Index scores and operative mortality ($P = 0{\cdot}211$) (*Table 1*). Patients with no Hardman Index risk factors appeared to be at low risk, with an operative mortality of 15 per cent. However, of nine patients with three or more Hardman Index risk factors, six survived aneurysm repair. The distribution of Hardman Index risk factors in this subgroup is shown in *Table 2*. Of the six survivors, four were discharged home, one was discharged to a spinal rehabilitation unit because of perioperative spinal cord ischaemia, and one was discharged to a community rehabilitation hospital. Median survival in this group was 35·5 (range 1–53) months.

Table 1 Distribution and mortality rates in 82 patients according to the Hardman Index

Hardman Index	0	1	2	≥3
No. of patients (%)	26 (32)	31 (38)	16 (20)	9 (11)
No. of deaths (%)	4 (15)	17 (55)	6 (38)	3 (33)

Table 2 Distribution of risk factors in nine patients with three or more Hardman Index variables

Hardman Index risk factor	Survivors ($n = 6$)	Died ($n = 3$)
Age (years)	76 (66–86)	79 (76–81)
Loss of consciousness	1 patient	1 patient
Creatinine (μmol/l)	215 (136–498)	208 (203–263)
Haemoglobin (g/dl)	8·3 (7·5–16·3)	11·4 (9·6–13·8)
ECG ischaemia	5 patients	2 patients

Values are median (range) unless otherwise stated.

Discussion

Subjecting patients at extreme operative risk to a futile attempt at repair of ruptured AAA has resource and ethical implications. Therefore most vascular surgeons in the UK advocate selective management of patients with ruptured AAA[8]. A scoring system that could identify patients with a ruptured AAA in whom operative intervention would be unsuccessful would be valuable, but a reliable instrument remains elusive. To deny operation to a patient based on an imprecise predictive tool would be a significant failing. For this reason, any potential scoring system requires comprehensive and robust validation.

In the present study, both the GAS and the Hardman Index appeared to lack validity. The GAS has recently been shown to be accurate when applied to elective AAA repair[9,10]. Samy and colleagues have previously reported on 92 patients with ruptured AAAs from three centres[5]. They concluded that a score higher than 95 was associated with a mortality rate of 80 per cent. In the present series, a score of 99 and above was associated with an operative mortality of approximately 40 per cent. Indeed, it was impossible to identify any score that conferred extreme risk, and even in 14 patients with scores of 110 or more operative mortality did not exceed 50 per cent. The Finnvasc Study Group have recently reported on a 9-year, retrospective series of 336 patients with a ruptured AAA from 21 hospitals. They showed that the GAS accurately predicted postoperative mortality, but they were unable to describe a cut-off value for patients at extreme risk[11].

The GAS was originally derived from an analysis of preoperative variables in patients with intact or ruptured AAA. Though it displays good fit as a predictive tool for elective AAA repair, it seems to be less reliable when used solely in patients with ruptured aneurysms, as seen in the present series. Its poor performance casts doubt over its use not only in outcome prediction but also as a risk-stratification tool for comparative audit of ruptured AAA mortality.

Until now, the Hardman Index has been reported to be accurate and has been recommended by four independent series[4,7,12,13]. Its appeal is heightened by its simplicity. It has been concluded that the presence of three or more Hardman risk factors in a patient represents a uniformly fatal prognosis. Combining these four series of 32 patients with three or more positive variables who underwent attempted aneurysm repair, all died apart from one, who survived to hospital discharge but succumbed 6 weeks later in a nursing home.

It was surprising that both scoring systems displayed such poor performance in the current data. If the Hardman Index had been used to select patients for operation in the present series, six patients would have been denied a life-saving operation; four of these patients were successfully discharged home. There may be several reasons for these differences. Though the present data were retrospective and susceptible to bias, so too were three of the four reports. The current series reported from a single high-volume centre on consecutive patients operated on by one of six surgeons during a contemporary 2-year study interval. The operative mortality in the current series is consistent with that regularly reported from this centre for ruptured AAA repair and may have influenced the performance of both the Hardman Index and GAS[6].

In contrast, preceding retrospective series have been drawn from longer study intervals or included non-consecutive patients[4,7,12]. The two prospective evaluations available in the literature pooled data from multiple centres[5,13]. The relationship between hospital and surgeon-volume and improved outcome has been established in elective AAA repair and is likely to be a factor in ruptured AAA repair[14,15]. In the Finnvasc Study Group data, most of the centres operated on fewer than ten ruptured AAAs each year; high-risk patients may be more likely to survive when managed in a high-volume centre[11].

The findings from the present study cast doubt over the validity of both the GAS and the Hardman Index as predictive tools in patients with ruptured AAA. Both scoring systems failed to predict mortality accurately in high-risk patients and neither can be recommended for routine use in clinical decision making. Further risk modelling with prospective validation is required to

dentify patients in whom operative intervention may be nappropriate.

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Original article

Cardiac troponin I predicts outcome after ruptured abdominal aortic aneurysm repair

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Background: Cardiac troponin I (cTnI) is a highly sensitive and specific marker for myocardial injury that predicts mortality in patients with acute coronary syndromes. This study examined the relationship between perioperative cTnI levels and clinical outcome in patients with ruptured abdominal aortic aneurysm (AAA).

Methods: Consecutive patients who underwent operative repair of a ruptured AAA over a 22-month interval and survived for more than 24 h were entered into a prospective observational cohort study. Levels of cTnI were measured immediately before, and at 24 and 48 h after surgery, and related to clinical outcome.

Results: Of 62 patients who underwent attempted operative repair of ruptured AAA, 50 (81 per cent) survived for more than 24 h and were included in this study. Twenty-three (46 per cent) of the 50 had a detectable cTnI level at one or more time points during the first 48 h. Of these, 11 patients had clinical or electrocardiographic evidence of an acute cardiac event and 12 did not; five patients in each of these two groups died. Of 27 patients with no increase in cTnI in the first 48 h, only three died ($P = 0{\cdot}031$ and $P = 0{\cdot}043$ respectively, relative to the groups with detectable cTnI).

Conclusion: Approximately half of patients who survived repair of ruptured AAA for more than 24 h sustained a detectable myocardial injury within the first 48 h. A perioperative increase in the level of cTnI, with or without clinically apparent cardiac dysfunction, was associated with postoperative death.

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Introduction

Abdominal aortic aneurysm (AAA) rupture continues to be associated with a high rate of perioperative morbidity and mortality. In patients who undergo technically successful repair of a ruptured aneurysm, death is generally attributed to the development of multiorgan failure, thromboembolic events and myocardial infarction[1]. Nevertheless, myocardial injury remains a frequently under-recognized complication.

Cardiac troponin I (cTnI) is a highly sensitive and specific marker for myocardial injury. In surgical patients it has been shown to identify perioperative myocardial infarction more accurately than the conventional creatinine kinase MB fraction isoenzyme[2]. In non-surgical patients with acute coronary syndromes, even small increases in cTnI are associated with an increased risk of death and reinfarction[3,4]. However, it remains uncertain whether perioperative myocardial injury after emergency aortic surgery, diagnosed on the basis of cTnI level, has the same prognostic implications as traditional markers of myocardial infarction.

This study examined the relationship between early perioperative myocardial injury, as detected by increased serum levels of cTnI, and clinical outcome after repair of ruptured AAA.

Patients and methods

Local research ethics committee approval was obtained for this study. Patients undergoing attempted operative repair of a ruptured AAA between October 2002 and July 2004 and who survived for more than 24 h were included in a prospective observational cohort study. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood. Demographic and clinical variables were recorded for all patients. Preoperative

cardiac and postoperative physiological risk stratification was carried out using the Detsky cardiac risk index[5] and the Acute Physiology And Chronic Health Evaluation (APACHE) II score[6] respectively. All patients underwent surgery by one of five consultant vascular surgeons.

Blood was sampled for cTnI on admission to the emergency room and on the first and second days after operation. These time points were chosen as representing the period of greatest risk of cardiac complications after vascular surgery[7]. Samples were collected in sterile lithium heparin tubes (Sarstedt, Nümbrecht, Germany) and analysed using an automated immunometric assay (Ortho-Clinical Diagnostics, Amersham, Bucks, UK). The 10 per cent coefficient of variation was 0·3 μg/l.

Primary outcomes assessed were postoperative death, defined as death in hospital or within 30 days of operation, and perioperative cardiac dysfunction. Cardiac dysfunction was determined on the following clinical and electrocardiographic grounds: prolonged cardiac chest pain, signs or symptoms of congestive heart failure, and electrocardiographic changes indicating ischaemia or a new persistent arrhythmia. Echocardiography was performed only when indicated clinically. Secondary outcomes included duration of mechanical ventilation, duration of critical care unit stay (intensive care or high-dependency units) and total hospital stay.

Statistical analysis

Statistical analysis was performed using SPSS® for Windows release 11.0.0 (SPSS, Chicago, Illinois, USA). Univariate analyses between groups were conducted using χ^2 or Fisher's exact test for categorical variables and Mann–Whitney *U* test for non-parametric continuous variables. $P \leq 0{\cdot}050$ was considered statistically significant.

Results

Eighty consecutive patients were admitted with a ruptured AAA. Of these, 62 (78 per cent) underwent attempted open repair; 18 (22 per cent) were deemed unsuitable for operation owing to co-morbidity. Of the 62 patients who had an operation, 11 (18 per cent) died during surgery and one died soon after admission to the intensive care unit. Preoperative cTnI levels were normal in these 12 patients. The remaining 50 patients (81 per cent) survived for at least 24 h and all but one survived for more than 48 h. There were 44 men and six women of median age 71 (range 53–87) years. Forty-two patients (84 per cent) had a contained retroperitoneal rupture and eight (16 per cent) had free intraperitoneal blood at laparotomy. Twelve patients (24 per cent) required temporary cross-clamping of the suprarenal aorta and the remainder were managed with control of the infrarenal aorta. Thirty-eight patients (76 per cent) had an aortic tube graft inserted and 12 (24 per cent) required a bifurcated graft. No patient was dependent on dialysis before operation but 19 (38 per cent) had evidence of pre-existing renal insufficiency (serum creatinine level more than 150 μg/l).

Twenty-three patients (46 per cent) had a detectable level of cTnI at one or more time points during the first 48 h after operation. Only two of these patients had a raised level of cTnI on admission, both of whom had a preoperative serum creatinine concentration greater than 150 μg/l. Twenty-two of the 23 patients had raised cTnI levels by the first day after surgery. There were no significant differences in Detsky cardiac risk index or APACHE II scores between patients, with and without a perioperative increase in cTnI (*Table 1*).

Of the 23 patients with a raised level of cTnI, 11 had clinical or electrocardiographic evidence of acute cardiac dysfunction during the first 48 h after operation. The remaining 12 did not have any clinically apparent cardiac events despite an increased cTnI level. Patients with occult cardiac dysfunction had significantly lower median (range) cTnI levels than those with a clinically evident cardiac event: 0·52 (0·28–1·65) *versus* 12·7 (1·31–67·5) μg/l ($P < 0{\cdot}001$).

Thirteen (26 per cent) of 50 patients died after surgery. Ten of these patients had a raised perioperative level of cTnI, five of whom had clinical evidence of a cardiac event and five with no apparent cardiac dysfunction. The

Table 1 Demographic and clinical variables in 27 patients without, and 23 patients with raised perioperative levels of cardiac troponin I

	cTnI negative ($n = 27$)	cTnI positive ($n = 23$)	*P*
Women	3	3	0·834†
Age (years)*	69 (53–87)	75 (63–82)	0·031‡
Detsky cardiac index*	15 (10–30)	15 (10–65)	0·147‡
Preoperative serum creatinine > 150 μg/l	6	13	0·013†
Suprarenal aortic clamp	4	8	0·183†
Blood loss (ml)	3000 (1325–8500)	4600 (1070–21 000)	0·062‡
Bifurcated graft	4	8	0·183†
APACHE II score*	16 (18–33)	19 (10–30)	0·065‡

*Values are median (range). cTnI, cardiac troponin I; APACHE, Acute Physiology And Chronic Health Evaluation. †Fisher's exact test; ‡Mann–Whitney *U* test.

cause of death was multiorgan failure in seven patients and respiratory failure in three. There were only three deaths among the 27 patients who had no perioperative increase in cTnI, significantly fewer than in both groups of patients with raised cTnI levels ($P = 0{\cdot}031$ and $P = 0{\cdot}043$, respectively). One patient died from multiorgan failure on the fourth day after surgery, one from respiratory failure at 38 days and one from an aortoenteric fistula at 46 days after operation.

Patients with raised levels of cTnI who survived spent significantly longer in intensive care and high dependency than those with no perioperative cTnI increase ($P = 0{\cdot}038$). Total stay in hospital and duration of mechanical ventilation were not significantly different between the two groups (*Table 2*).

Discussion

A previous non-consecutive series of selected patients undergoing ruptured AAA repair in this hospital had an incidence of perioperative myocardial injury in excess of 50 per cent[8]. Present data confirm that around half of the patients who survive repair of a ruptured AAA sustain a detectable perioperative myocardial injury. Of these, roughly half have a clinically silent event, with a low-level cTnI increase. By comparison, approximately a quarter of patients who undergo a major vascular surgical operation develop perioperative myocardial injury, as determined by raised levels of cardiac troponins[2]. The incidence of myocardial injury in critically ill patients in intensive care is similarly reported to be between 15 and 40 per cent[9–11]. Patients with a ruptured AAA are subject to a greater risk of perioperative cardiac injury. This is likely to reflect the impact of massive haemorrhage and transfusion, compounded by the burden of cardiovascular co-morbidity that is common in these patients. In the present series, however, preoperative cardiac status, as assessed by the Detsky risk index, was not associated with postoperative myocardial injury. The sample size of this series did not permit a multivariate analysis of perioperative variables associated with myocardial injury and outcome.

Cardiac troponins are the standard biomarker for the diagnosis of myocardial infarction and a useful tool for risk stratification in patients with acute coronary syndromes[12,13]. Levels of cardiac troponins may also be raised in other clinical conditions and have similar prognostic value in patients with sepsis, renal failure and pulmonary embolism[14]. It is now acknowledged that even minor increases in cardiac troponin, below the diagnostic criteria for myocardial infarction, are indicative of increased clinical risk[15]. The present study demonstrated that a slight, clinically silent increase in cTnI level within the first 48 h after operation conferred an increased risk of postoperative death. In contrast, only one of 27 patients without a rise in cTnI died within 30 days of operation. In terms of secondary outcomes, patients with raised cTnI levels also required a significantly longer stay in critical care. Although total stay was not significantly increased in such patients, it is recognized that hospital stay, unlike critical care, may be influenced by circumstances unrelated to a patient's clinical condition.

The question remains whether raised cTnI levels represent a marker of severity of critical illness and its consequent adverse outcome, or whether there is a causal relationship between myocardial dysfunction and subsequent morbidity and mortality. The possible mechanisms underlying raised cardiac troponin levels, apart from myocardial necrosis, include leakage of cardiac proteins from myocyte cell membranes[14]. Tumour necrosis factor (TNF) α is known to increase endothelial permeability and may also be implicated at the cardiac myocyte level[16,17]. Patients who survive initial repair of a ruptured AAA develop a postoperative systemic inflammatory response syndrome with an associated increase in circulating TNF-α levels[18,19]. It has been reported that high levels of TNF-α are associated with poor outcome after ruptured AAA repair[19]. Thus, an increase in cTnI and myocardial dysfunction may be an effect of an underlying systemic inflammatory response.

Table 2 Outcomes in 27 patients without, and 23 patients with raised perioperative levels of cardiac troponin I

	cTnI negative	cTnI positive	*P**
Survivors and non-survivors			
Critical care stay (days)	3 (1–38)	6 (1–46)	0·031
Duration of ventilation (days)	1 (1–38)	2·5 (1–43)	0·008
Total hospital stay (days)	14 (4–56)	12 (1–58)	0·711
Survivors			
Critical care stay (days)	3 (1–11)	5 (1–42)	0·038
Duration of ventilation (days)	1 (1–5)	1 (1–38)	0·199
Total hospital stay (days)	14 (7–56)	18 (8–58)	0·202

Values are median (range). CTnI, cardiac troponin I. *Mann–Whitney *U* test.

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Functional outcome after open repair of ruptured abdominal aortic aneurysm

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Background: **Outcome after operative repair of ruptured abdominal aortic aneurysm (AAA) has traditionally been assessed in terms of survival. This study examines the functional outcome of patients who survive operation.**
Methods: **Consecutive patients who survived open repair over an 18-month period were entered into a prospective case-control study. Age- and sex-matched controls were identified from patients undergoing elective AAA repair. The Short Form-36 health survey was administered to both groups of patients at 6 months after operation. Results were compared with the expected scores for an age- and sex-matched normal UK population.**
Results: **Fifty-seven patients underwent open repair of a ruptured AAA, and 30 survived; no patient was lost to follow-up. There were no significant differences in quality of life between patients who had an emergency repair and those who had an elective repair. Both of these groups had poorer health-related quality of life outcomes than the matched normal population. Surprisingly, compared with the normal population, patients after elective repair had poorer outcomes in more health domains than patients who survived emergency operation.**
Conclusions: **Survivors of ruptured AAA repair have a good functional outcome within 6 months of operation. (J Vasc Surg 2005;41:758-61.)**

Open repair of ruptured abdominal aortic aneurysm (AAA) is burdened with high perioperative morbidity and mortality. Furthermore, its cost in financial terms and resource utilization is significant.[1] Although survivors may return to a normal life expectancy, their functional outcome, in terms of health-related quality of life (HRQoL), remains uncertain. In properly assessing the value of a surgical intervention, functional outcome must be examined alongside the more traditional outcome measures of operative morbidity and mortality. If a survivor of ruptured AAA were returned to a significant level of functional disability despite a near-normal life expectancy, the benefit of intervention would become less apparent. To quantify the efficacy of ruptured AAA repair with accuracy, HRQoL analysis is essential.

Published data on HRQoL after aneurysm rupture are limited. Although it has been suggested that survivors of ruptured AAA repair regain their preoperative quality of life, this rests on retrospective data of uncertain validity.[2-15] A recent review of HRQoL after repair of ruptured aneurysm concluded that prospective data are now needed.[16] This study examines the postoperative HRQoL of survivors of ruptured AAA repair when compared with that of patients undergoing elective AAA repair and that of the general population.

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METHODS

Local Research Ethics Committee approval was obtained for this study. Patients undergoing open operative repair of a ruptured AAA over the 18-month period from September 2002 to March 2004 were included in a prospective observational case-control study. Patients were selected for operative intervention and were operated on by one of five vascular surgeons. Ruptured aneurysm was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause of hematoma other than an aneurysm at laparotomy. A control group of age- and sex-matched patients undergoing elective open repair of asymptomatic AAA during the study period was also identified. Endovascular aortic repair was not used as a therapeutic option for either intact or ruptured AAA during the study period. Demographic and clinical variables for both groups were recorded. The severity of illness was scored by using the Simplified Acute Physiology Score II recorded during the first 24 hours after operation.[17] Patient survival was confirmed by using hospital and general practice records.

The Short Form-36 Health Survey (SF-36; QualityMetric Inc, Lincoln, RI) is a generic HRQoL instrument and comprises 36 questions studying 8 domains of health: physical functioning, social functioning, role limitations due to physical problems, role limitations due emotional problems, mental health, pain, vitality, and general health perception. Each domain scores from 0 to 100, with higher scores representing a better quality of life. The reliability, validity, and consistency of the SF-36 have been confirmed, and its use in the assessment of vascular and aneurysm disease has been recommended.[18,19]

The self-administered UK version of the SF-36 was sent to all patients 6 months after aneurysm repair. This time point was chosen as representing the time by which patients

undergoing elective AAA repair regain their preoperative levels of HRQoL.[18] Repeat questionnaires were sent after 2 weeks if no reply was received. Questionnaires were scored according to the methods described by Ware et al.[20] Mean scores and standard deviations were calculated for each group and compared. Further comparison was made between the age- and sex-matched general population data for the United Kingdom.[21]

Statistical analysis was performed with SPSS for Windows release 11.0.0 (SPSS Inc, Chicago, Ill). Between-groups differences were determined by the unpaired t test or Mann-Whitney U test for parametric and nonparametric continuous variables, respectively; $P \leq .05$ was considered significant.

RESULTS

Seventy-three consecutive patients were admitted with a ruptured AAA during the study period, of whom 57 (78%) underwent attempted aneurysm repair. Reasons for nonoperative management are listed in Table I. Of these 57, 30 (53%) survived to discharge from the hospital and were included in this study. There were 26 men and 4 women of median age 68 years (range, 53-85 years). Twenty-two of the 30 patients had hemodynamic instability, as defined by a preoperative blood pressure of less than 90 mm Hg, before operation. During the same period, 78 patients underwent elective repair of an asymptomatic aneurysm, and 19 underwent urgent repair of an acutely symptomatic aneurysm. Thirty patients with asymptomatic AAA were selected as suitable age- and sex-matched controls. The median age of the 26 male and 4 female control patients was 70 years (range, 59-83 years; $P = .440$). Patients who had repair of a ruptured aneurysm had a median hospital stay of 14 days (range, 7-59 days), whereas patients undergoing elective operation stayed for a median of 11 days (range, 7-37 days; $P = .048$). The median Simplified Acute Physiology Score II for patients undergoing ruptured AAA repair was 30 (range, 18-52), and for patients who had elective repair, it was 16 (range, 12-30; $P < .001$).

At the 6-month follow-up, all patients in both the study and control groups were still alive. Twenty-eight of the 30 patients who survived ruptured aneurysm repair had been discharged to their homes, one patient required nursing home care, and one remained in a geriatric rehabilitation unit. All patients in the control group were discharged home. The SF-36 questionnaire was self-administered by all but one patient, who required the aid of a proxy. All patients from both groups returned a completed form.

Comparisons of SF-36 scores of the ruptured AAA, elective AAA, and normal populations are shown in Tables II to IV. There was no statistically significant difference between patients who had undergone ruptured aneurysm repair or an elective aneurysm repair in any of the health domains. However, when HRQoL in survivors of aneurysm rupture was compared with that of the matched normal population, the former group had significantly worse outcomes in terms of role limitations due to physical and emotional problems. There were no statistically significant differences in the other six health domains. In contrast, comparison of functional outcome between patients who underwent elective repair and the normal population showed the former group to have significantly worse outcomes in the domains of physical function, bodily pain, and social functioning, as well as role limitations due to physical and emotional problems.

Table I. Primary reason for refusal of surgery in 16 patients

Reason for refusal	*No. patients*
Cardiac arrest/refractory LOC	7
Age-related comorbidity	5
Cardiorespiratory comorbidity	2
Malignancy	1
Dementia	1

LOC, Loss of consciousness.

Table II. Mean (SD) SF-36 scores in 30 patients after ruptured AAA repair and in 30 patients after elective AAA repair

Health domain	*Ruptured AAA repair*	*Elective AAA repair*	P *value*
Physical function	65 (27)	55 (30)	.222
Role limitations physical	58 (29)	57 (33)	.855
Bodily pain	69 (28)	60 (28)	.196
General health	62 (24)	63 (22)	.770
Vitality	55 (23)	54 (24)	.911
Social functioning	78 (32)	71 (31)	.441
Role limitations emotional	68 (33)	71 (35)	.733
Mental health	77 (19)	76 (17)	.782
Mental summary score	49 (12)	49 (12)	.842
Physical summary score	44 (11)	40 (11)	.297

SF-36, Short Form-36 Health Survey; *AAA*, abdominal aortic aneurysm.

DISCUSSION

Postoperative quality of life is a frequently neglected outcome measure in the assessment of surgical interventions. In contrast, oncologic interventions have been routinely subjected to HRQoL analysis, and the UK Medical Research Council has introduced HRQoL measures into their guidelines for clinical trials.[22,23] Ruptured AAA repair, and subsequent recuperation, is associated with a major physical and psychological insult. Nevertheless, there are few data on functional outcomes in this situation. This series contains the first prospective data examining HRQoL after ruptured aneurysm repair. Although the limitations of the data are acknowledged inasmuch as preoperative assessment of HRQoL is absent and the sample size is relatively small, the nature of ruptured AAA does not allow the former, and only three retrospective series have individually reported more patients.[5,6,12] Multivariate analysis on current data to identify independent predictors of functional outcome has not been performed because the small sample size renders such analysis vulnerable to type II statistical error.

Table III. Mean (SD) SF-36 scores in 30 patients after ruptured AAA repair and the age- and sex-matched normal population

Health domain	*Ruptured AAA repair*	*Normal population*	P *value*
Physical function	65 (27)	72 (9)	.162
Role limitations physical	58 (29)	72 (5)	.016
Bodily pain	69 (28)	77 (3)	.167
General health	62 (24)	64 (2)	.638
Vitality	55 (23)	62 (4)	.116
Social functioning	78 (32)	83 (4)	.339
Role limitations emotional	68 (33)	87 (4)	.004
Mental health	77 (19)	79 (2)	.521

SF-36, Short Form-36 Health Survey; *AAA,* abdominal aortic aneurysm.

Table IV. Mean (SD) SF-36 scores in 30 patients after elective AAA repair and the age- and sex-matched normal population

Health domain	*Elective AAA repair*	*Normal population*	P *value*
Physical function	55 (30)	72 (9)	.007
Role limitations physical	57 (33)	72 (5)	.019
Bodily pain	60 (28)	77 (3)	.003
General health	63 (22)	64 (2)	.926
Vitality	54 (24)	62 (4)	.098
Social functioning	71 (31)	83 (4)	.043
Role limitations emotional	71 (35)	87 (4)	.018
Mental health	76 (17)	79 (2)	.253

SF-36, Short Form-36 Health Survey; *AAA,* abdominal aortic aneurysm.

Present data show that the quality of life of survivors of ruptured AAA is no different from that of patients who have undergone elective aneurysm repair. Furthermore, this recovery in functional performance is apparent within 6 months of operation. It is interesting that functional recovery is so similar between two groups that are clearly different in terms of illness severity and hospital stay. The 30 patients with ruptured aneurysm are a highly selected group who have survived to reach the hospital, have been selected for operative intervention, have survived operation, and have survived to the 6-month follow-up. Survival after aneurysm rupture is influenced by good preoperative physiological status, and this may predispose these patients to achieving good functional outcomes.[24] Existing studies of HRQoL after elective open repair of AAA have shown that patients regain their preoperative functional status within 3 to 6 months of operation.[18,25] It would seem, from the present data, that recovery of HRQoL after ruptured aneurysm repair follows a similar time course. However, if HRQoL assessment had been performed at an earlier time point from operation, differences in functional outcome may have been apparent.

Eight previously published series[2,3,5-7,9,14,15] compared HRQoL outcome after ruptured and elective AAA repair. All were retrospective and had a varying duration of follow-up, thus rendering them vulnerable to an even greater selection bias. In contrast, the present prospective data describe a consecutive series of patients with ruptured AAA with a fixed follow-up interval. All but one of the preceding retrospective studies concluded that ruptured aneurysm survivors regain a quality of life similar to that of patients undergoing elective AAA repair. Magee et al[6] are the only authors to have demonstrated a significant deterioration in functional outcome after ruptured AAA repair compared with elective repair. They reported a decrease from near-perfect HRQoL to considerable disability after ruptured aneurysm repair. However, in their series, patients who underwent elective repair were not matched for age and, in fact, were much younger than the patients with ruptured AAA. It is noteworthy that there is relative consistency in SF-36 health domain scores between the present data and the three other studies that have used this instrument.[8,10,11] Such a finding across different series supports the conclusion that survivors of ruptured AAA do regain a good quality of life. Although a selective policy of operative intervention has governed this series, the good functional outcomes attained do justify an aggressive policy of surgical intervention for ruptured aneurysm.

The present series shows that survivors of ruptured aneurysm have poorer outcomes in terms of role limitations due to physical and emotional problems when compared with the general population. It is, perhaps, unsurprising that they have some functional disability after such a major surgical intervention. However, no other differences were demonstrated in the other health domains. It is interesting to note that functional outcome after elective aneurysm repair displayed poorer outcomes in more health domains—physical functioning, bodily pain, and social functioning. Taking these results at face value, one would infer that patients who survived ruptured aneurysm repair had a better functional outcome than those who had an elective operation. This, clearly, is counterintuitive. It is likely that this discrepancy is related to the selection of biologically robust individuals for emergency operation; they survive to have a good functional recovery after surgery. A possible alternative is that a near-death experience has a positive effect on an individual's perception of his or her functional performance, resulting in a higher rating of HRQoL.

This study provides benchmark HRQoL data for patients who survive open repair of ruptured AAA. In the future, functional outcomes after endovascular repair can be assessed against these results.

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World Journal of Surgery

;ystemic Inflammation and Repair of Abdominal Aortic ıneurysm

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bstract

ackground Inflammation is integral to the pathogenesis f abdominal aortic aneurysm (AAA). This study examines 'eoperative biomarkers of systemic inflammation in pa- ents undergoing open repair of intact and ruptured AAA.

lethods One-hundred twelve patients were entered into a 'ospective observational study. Preoperative POSSUM ıysiology score, C-reactive protein (CRP), white blood ɔunt (WBC), platelet count, fibrinogen, and albumin were :corded and related to clinical variables using univariate ıalysis.

esults Sixty-one patients with a ruptured AAA, 39 with ı asymptomatic intact AAA, and 12 with an acutely /mptomatic intact AAA underwent attempted repair. here were two inflammatory asymptomatic aneurysms ıd one inflammatory ruptured aneurysm. No patient had inical evidence of coexistent inflammatory disease. Pa- ents with a symptomatic intact AAA had a significantly 'eater level of CRP and fibrinogen, higher WBC, and lower serum albumin, than those with an asymptomatic intact AAA. Patients with a ruptured aneurysm had a significantly greater level of CRP, higher WBC, and lower serum albumin than those with an asymptomatic intact aneurysm. Patients with a symptomatic intact AAA had a significantly higher CRP level, but lower WBC, than those with a ruptured AAA. There was no difference in CRP level, WBC, or serum albumin between survivors and nonsurvivors of attempted repair of asymptomatic, symptomatic and ruptured AAA.

Conclusions Acutely symptomatic and ruptured AAAs are associated with an early elevation in systemic inflammatory biomarkers. This early activation of the inflammatory response might influence perioperative outcome.

Inflammation is an integral factor in the pathogenesis of abdominal aortic aneurysms (AAA) histologically characterized by a transmural infiltration of macrophages and lymphocytes. These cells are thought to elicit an inflammatory cytokine cascade, culminating in the degeneration of aortic connective tissue [1]. Interestingly, patients with AAA have elevated serum markers of inflammation and the acute phase response when compared with healthy controls and controls with coexistent vascular disease [2, 3]. Furthermore, serum concentrations of inflammatory cytokines are associated with aneurysm diameter and rate of expansion [4]. However, the precise relationship between systemic markers of inflammation, the acute phase response, and aortic aneurysms is uncertain.

C-reactive protein (CRP) is an acute-phase protein that is a strong, independent risk factor for atherosclerosis [5]. It may also predict survival in critically ill patients and in patients with underlying neoplasia [6, 7]. It is unclear whether inflammatory biomarkers have any such prognostic significance in patients undergoing AAA repair.

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ystemic inflammatory proteins may have a role as a agnostic tool or as a means of preoperative risk stratifi-ıtion.

This study compares easily measured preoperative ıflammatory biomarkers in patients admitted for open pair of intact and ruptured AAA, and their relationship ith clinical outcome.

Iaterials and Methods

ɔcal Research Ethics Committee approval was obtained ·r this research. Consecutive patients admitted for open pair of intact (September 2003–September 2004) or ıptured (January 2003–September 2004) AAA were in-uded in a prospective observational case-cohort study. hose with intact AAA were further stratified into an ;ymptomatic group undergoing elective repair and an :utely symptomatic group requiring urgent operation. An :utely symptomatic aneurysm was typified by severe back ıd/or abdominal pain, hemodynamic stability, and ten-:rness of the AAA on palpation. Ruptured aneurysm was 'pified by the presence of retroperitoneal and/or intra-:ritoneal blood at laparotomy in the absence of any entifiable cause other than an aneurysm. Patients were agnosed as having an inflammatory AAA by operative ɔpearance. An inflammatory AAA was characterized by e presence of a thickened aneurysmal wall, perianeur-;mal fibrosis, and adhesions to adjacent structures [8]. emographic and clinical variables for all patients were corded. Preoperative physiological status was stratified :cording to the Physiological and Operative Severity :ore for the enUmeration of Mortality and morbidity 'OSSUM) [9]. All patients were operated on by one of ve consultant vascular surgeons.

Blood was sampled for the following biomarkers of flammation: CRP, platelet count, white blood cell count, ɔrinogen, and albumin. Serum samples were collected at e time of admission in sterile, lithium heparin, potassium -DTA, or sodium citrate tubes (Sarstedt AG & Co. Nümbrecht, Germany) and analyzed in the Clinical Biochemistry and Haematology Laboratories of the Royal Infirmary of Edinburgh. C-reactive protein analysis was performed with an automated immunoturbidimetric assay (Abbott TDX, Abbott Laboratories, Maidenhead, UK). A systemic inflammatory response was defined by a CRP level of > 10 mg/l [10]. Primary outcome was assessed in terms of postoperative mortality, defined as death in-hospital or within 30-days of operation.

Statistical analysis was performed using SPSS for Windows Release 13.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses between groups were determined by the chi-square or Fisher's exact test for categoric variables and by the Kruskal-Wallis and Mann-Whitney U-test for non-parametric continuous variables. Spearman's rank correlation coefficient was calculated to assess the strength of association between continuous variables; $p \leq 0.05$ was considered significant.

Results

Fifty-one consecutive patients, 39 asymptomtatic and 12 acutely symptomatic, underwent attempted repair of an intact aneurysm, and 61 of a ruptured aneurysm, during the study period. Demographic and clinical variables are shown in Table 1.

There was no statistically significant difference in age ($p = 0.876$), gender ($p = 0.275$), aneurysm diameter ($p = 0.871$), or POSSUM physiology score ($p = 0.201$) between patients with an asymptomatic or symptomatic intact AAA. Patients with ruptured AAA had larger aneurysms on selectively utilized computed tomography (CT) or ultrasound scan ($p = 0.007$) and higher POSSUM physiology scores ($p < 0.001$) than those with asymptomatic lesions; age ($p = 0.470$) and gender ($p = 0.609$) distribution were, however, similar.

There were no statistically significant differences in age ($p = 0.457$), gender ($p = 0.257$) or AAA size ($p = 0.197$) between patients with ruptured AAA and those with

able 1 Demographic and clinical variables in 112 patients undergoing open repair of abdominal aortic aneurysm (AAA)

	Asymptomatic AAA ($n = 39$)	Symptomatic AAA ($n = 12$)	Ruptured AAA ($n = 61$)
ge (years)	72 (48–87)	71 (64–84)	72 (53–87)
ale sex	34	9	53
OSSUM physiology score	19 (14–28)	23 (13–35)	33 (15–55)
AA size (cm)	6.1 (4.7–10)	6.3 (3.4–9)	7.5* (4.5–10)
flammatory AAA	2 (5%)	0	1 (2%)

alues are median (range) or number (%)

Selectively performed preoperative imaging

able 2 Inflammatory biomarkers in 112 patients with AAA

	Asymptomatic AAA (n = 39)	Symptomatic AAA (n = 12)	Ruptured AAA (n = 61)	p Value
RP (mg/l)	< 5 (< 5–22)	22 (5–103)	7 (< 5–168)	< 0.001
BC × 10^9/l	7.0 (4.4–13.7)	8.8 (5.4–19.2)	13.2 (4.4–24.0)	< 0.001
atelets ×10^9/l	209 (125–320)	240 (123–428)	186 (89–462)	0.008
brinogen (g/l)	3.6 (2.1–6.0)	4.6 (2.1–6.7)	2.8 (0.2–5.5)	< 0.001
bumin (g/l)	41 (34–47)	37 (27–47)	33 (18–47)	< 0.001

alues are median (range). Kruskal-Wallis test

mptomatic intact aneurysms; however, POSSUM physiology scores (p = 0.001) were greater in the former group. o patient had clinical evidence of a significant coexistent flammatory disease, and the distribution of inflammatory AAs, as determined at laparotomy, is shown in Table 1.

There were significant differences in CRP level, fibrinogen level, WBC count, and platelet count across the three oups of patients (Table 2). Asymptomatic intact AAAs ere associated with a lower CRP level (p < 0.001), rinogen level (p = 0.022), and WBC count (p = 0.036), id with a higher serum albumin level (p = 0.017) than mptomatic intact aneurysms; platelet counts were similar = 0.152). Asymptomatic lesions were also associated ith lower CRP level (p = 0.002) and WBC count (p < 001), and with higher serum albumin (p < 0.001), than ptured AAA. However, patients with asymptomatic AAA id greater platelet counts (p = 0.026) and fibrinogen levels = 0.005) than those with ruptured aneurysms.

Patients with symptomatic intact AAA had higher CRP vels (p = 0.042) but a lower WBC count (p = 0.04) than ose with ruptured lesions. Platelet count (p = 0.011) and rinogen level (p = 0.01) were higher with symptomatic tact aneurysms. There was no difference in serum albumin between groups (p = 0.171). Analysis of all patients ith AAA failed to demonstrate any correlation between ge (r = 0.139, p = 0.157) or aneurysm size (r = 0.010, p = 930) and CRP. However, POSSUM physiology score rrelated with CRP (r = 0.283, p = 0.004). The distribution systemic inflammatory response as defined by serum RP levels is shown in Table 3. Patients with symptomatic ruptured AAA were more likely to have a systemic flammatory response (p < 0.001).

ble 3 Presence (CRP > 10 mg/) or absence (CRP ≤ 10 mg/l) of a stemic inflammatory response in 106 patients

	Asymptomatic AAA	Symptomatic AAA	Ruptured AAA
RP ≤ 10 mg/l	31 (86%)	2 (18%)	32 (54%)
RP > 10 mg/l	5 (14%)	9 (82%)	27 (46%)
Value	<0.001		

lues are number (%). Chi-square test

Table 4 Causes of perioperative death in 30 patients

	Asymptomatic AAA	Symptomatic AAA	Ruptured AAA
Multiorgan failure	1	1	11
Intraoperative death	1	–	11
Myocardial infarction	1	–	2
Respiratory failure	–	1	1
Aorto-enteric fistula	–	–	1

There were 3 (8%), 2 (17%), and 21 (41%) perioperative deaths in the asymptomatic, symptomatic, and ruptured AAA groups, respectively. Causes of deaths are shown in Table 4. There was no statistically significant difference between survivors and non-survivors of AAA repair in terms of systemic inflammatory response, CRP level, WBC, or serum albumin in any of the three groups. Those who survived ruptured AAA repair had higher platelet counts (p = 0.006) and serum fibrinogen levels (p = 0.002) than those who died.

Discussion

The systemic inflammatory response is typified by the synthesis of proteins by the liver [11]. The effect is mediated by proinflammatory cytokines. Proteins such as CRP and fibrinogen increase, while others such as albumin fall. Most AAAs exhibit features of inflammation on histological examination, and increased expression of local and circulating proinflammatory cytokines is well documented in patients with aneurysms [12–14]. Controversy persists about the extent to which this cytokine upregulation evokes a systemic inflammatory response and about the influence of aneurysm symptomatology on this process [4].

This study shows that patients with symptomatic intact or ruptured AAA have elevated markers of systemic inflammation before operative intervention. Both the CRP

ıd the WBC levels were significantly higher than those ıcountered in patients with asymptomatic AAA. The imulus for this inflammatory response is uncertain. learly, ruptured AAA causes acute hemorrhage and hyɔvolaemic shock as inflammatory triggers. However, ′mptomatic intact lesions do not result in such a profound ıysiological insult; a lower POSSUM physiology score flects this. However, pain is a cardinal feature of flammation and in acutely symptomatic AAA is thought relate to a sudden expansion in aneurysm size [15]. This sser trigger seems capable of evoking systemic changes circulating inflammatory biomarkers too. This elevation easily measured serum markers of inflammation supɔrts their utility as diagnostic tools in patients with acute ɔrtic pathology. While nonspecific, their use in conjuncɔn with clinical evaluation may prove a valuable indicator impending or established aneurysm rupture. Interpretaɔn of changes in the other inflammatory markers is conɔunded by a number of factors. Acute blood loss and the lutional and volume redistribution effects of intravenous ıid resuscitation may influence changes in platelet count ıd fibrinogen level [16]. The use of these inflammatory arkers as diagnostic or prognostic tools is limited by such ctors.

Despite similar physiological scoring, and the integrity the aneurysm being preserved, patients with symptomic lesions had an operative mortality rate more than twice at of patients undergoing repair of an asymptomatic AA. Reasons for the increased operative mortality assoated with symptomatic aneurysms, though well deribed, remain unresolved [17]. However, it is possible at elevated systemic inflammatory proteins in symptomic patients may be implicated.

Multiple organ failure is a major cause of perioperative ɔath after AAA repair [18]. Excessive activation of flammatory pathways and release of inflammatory cytones underpin organ dysfunction. An initial inflammatory imulus, such as acute AAA expansion or rupture, may ıuse priming of inflammatory pathways. A subsequent imulus, such as ischemia-reperfusion injury during ıeurysm repair, causes an inflammatory response greater an expected if it occurred in isolation [19]. Such a pheɔmenon might partially account for the increased morlity rates found in patients with acute AAA.

If a primed inflammatory response were related to ɔrioperative death in patients with acute AAA, it would be ıticipated that raised CRP levels would be associated with ɔath. However, the present data have shown that neither RP level nor a systemic inflammatory response provides ognostic information in terms of survival after AAA reıir. In contrast, Schillinger and colleagues have reported at admission CRP levels predict poor outcome [20]. Their trospective series combined patients with thoracic and abdominal aortic disease, including both aortic dissections and aneurysm. Despite the heterogeneity of their sample population, they concluded that CRP level was useful for risk prediction in acute aortic disease. The absence of such an association in the present series is surprising considering the positive correlation between preoperative physiological status, as reflected by POSSUM score, and CRP level (patients with greater physiological compromise had higher CRP levels). It is possible that the failure of CRP to predict mortality in the present data is a reflection of small sample size. Alternatively, the use of newer high-sensitivity CRP assays may have yielded greater prognostic information. Furthermore, analysis of the temporal changes in inflammatory markers in the postoperative period may also have conferred useful prognostic information.

These data highlight the presence of an early elevation in inflammatory biomarkers and the systemic inflammatory response in patients before elective and emergency aortic aneurysm repair. This inflammatory process and upregulation of the acute phase response might affect perioperative outcome.

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'redictors of Outcome After Abdominal Aortic Aneurysm Rupture: Edinburgh Ruptured Aneurysm Score

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bstract

ackground Many surgeons adopt a selective policy of ıtervention for a ruptured abdominal aortic aneurysm AAA). This study aimed to develop an objective method -f identifying patients suitable for attempted repair.

Methods Consecutive patients selected for attempted epair of ruptured AAA over a 31-month period (January 000 to July 2002) were entered into an observational study. \ltogether, 53 preoperative physiological and biochemical ·ariables were recorded and related to operative outcome.

Results A total of 105 patients underwent attempted epair of a ruptured AAA. There were 39 (37%) deaths in ıospital or within 30 days of operation. On univariate nalysis, hemoglobin <9 g/dl ($p = 0.038$), blood pressure :90 mmHg ($p = 0.036$), and Glasgow Coma Scale <15 $v = 0.016$) were found to be risk factors that predicted eath. Of 70 patients with no or one risk factor, 20 (29%) lied. Of 30 patients with two factors, 15 (50%) died, and of he five patients with all three factors, four (80%) died. Chere was a significant association between mortality and :umulative risk factors ($p = 0.003$).

Conclusion These three risk factors are easily assessed in he emergency setting and might form the basis of a scoring ;ystem to inform the outcome of ruptured AAA.

Despite increased elective abdominal aortic aneurysm (AAA) repair, the incidence of ruptured AAA is increasing in Europe [1, 2]. Disconcertingly, aneurysm rupture continues to be associated with a prohibitive mortality rate, with 50% of patients who reach a hospital not surviving [3]. Among them, some are already at an overwhelming risk of death due to coexisting morbidity or irreversibly compromised physiologic status. It is for this reason that most surgeons in the United Kingdom adopt a selective policy for intervention [4]. However, patient selection is largely based on subjective criteria, and there is conflicting evidence about which variables to base objective preoperative outcome prediction in patients with a ruptured AAA [5, 6].

Previously reported data from this center have shown that the two most popular preoperative risk-scoring methods (Hardman Index, Glasgow Aneurysm Score) lack validity, and this finding has now been confirmed by other centers [7–11]. Reasons for this lack of fit may be related to the fact that the existing models derive from clinical data that are mostly two decades old and that were accumulated over long study periods. Furthermore, they include results from low-volume institutions. Their use cannot be robustly recommended for the purpose of clinical decision-making. The present study aimed to examine preoperative variables associated with perioperative death in a large, contemporary series of patients from a high-volume center. These variables were modeled to develop an objective risk-scoring instrument with which to inform patient selection.

Method

All patients admitted to the Edinburgh Vascular Surgical Service who underwent repair of a ruptured AAA over a 31-month period (January 2000 to July 2002) were identified from a prospective database and included in an

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etrospective observational study. The database, together /ith hospital records, provided demographic details and linical and operative information for all patients under- oing attempted repair. Operation was defined as the elivery of an anesthetic with the intention of performing AA repair. Ruptured aneurysm was defined as the pres- ıce of retroperitoneal and/or intraperitoneal blood in the)sence of any other identifiable cause for hematoma other an an aneurysm [12].

All patients were operated on by one of seven consultant ıscular surgeons. An open transperitoneal repair was the vored surgical approach. The protocols observed in our ıit did not advocate the use of endovascular aortic repair)r emergency AAA repair during the study period. :lection for operation was at the discretion of the tending surgeon. Surgical intervention was not under- ken if the patient declined operation, if the patient had a ıown serious co-morbidity such as advanced malignancy, : if the patient was otherwise unsuitable (e.g., such as aving refractory loss of consciousness or cardiac arrest, aving severe dementia, or being dependent and requiring ursing home care). There were 53 preoperative variables lentified in other studies, or suspected on clinical grounds, ɔ be associated with mortality that were recorded for each atient and related to subsequent outcome.

Loss of consciousness was defined as an in-hospital vent; and the Glasgow Coma Scale (GCS) was defined as ıe best recorded level in hospital. Cardiac symptoms were ypified by previous myocardial infarction, anginal symp- ɔms, or symptoms of congestive cardiac failure. :espiratory symptoms were defined by dyspnea at rest or n exertion; and peripheral arterial occlusive disease PAOD) was defined by a history of intermittent claudi- ation or critical limb ischemia. Electrocardiographic ECG) ischemia was typified by >1 mm ST segment epression or an associated T-wave change on the admis- ion ECG.

Statistical analysis was performed using SPSS for Windows Release 13.0.0 software (SPSS, Chicago, IL, JSA). Univariate differences between categoric variables were compared using the chi-squared test with Yates' :orrection or Fisher's exact test. Univariate differences)etween groups for parametric and nonparametric contin- uous variables were determined by the unpaired Student's *t*-test and the Mann-Whitney U-test, respectively. A value of $p \leq 0.05$ was considered significant. Multivariate modeling examining the simultaneous and independent effect of the significant demographic and clinical charac- teristics was then carried out using logistic regression. A stepwise (forward–backward) variable selection procedure was adopted. Clinically relevant variables predictive of death were then modeled to develop a prognostic risk score for ruptured AAA. The chi-squared test for trend was used to compare the trend in the actual mortality rate as related to an increasing risk score.

Results

In toal, 129 consecutive patients were admitted with ruptured AAA during the study period. Among them, 105 (81%) underwent attempted open repair, and 24 (19%) were deemed unsuitable for operation due to prohibitive co-morbidity. Of the 105 patients undergoing attempted open repair, 91 were men and 14 were women. The mean ± SD age of the study population was 72 ± 7 years. Altogether, 47 (45%) patients were transferred from another hospital, and the remainder were referred directly to the vascular surgical service by their general practitioner, the Emergency Department, or another specialty in the authors' hospital.

A total of 19 patients required a secondary intervention following their aneurysm repair: 12 (11%) patients required a further laparotomy for hemostasis, 3 (3%) needed colonic resection, and 5 (5%) needed some other form of intervention; one patient required two secondary interventions. There were 39 (37%) deaths in hospital or within 30 days of operation. Altogether, 16 (15%) patients died during surgery of massive hemorrhage or cardiac arrest; 18 (17%) died of multiorgan failure, and 5 (5%) died of other causes. Of 66 surviving patients, 61 (92%) suffered one or more postoperative complications as defined by the Committee on Reporting Standards of the Society for Vascular Surgery and the North American chapter of the International Society for Cardiovascular Surgery [13].

Preoperative variables predictive of death after attempted repair of ruptured AAA are listed in Tables 1 and 2. Of the continuous variables, only hemoglobin level and blood pressure were predictive of perioperative death. These continuous variables were stratified to create categoric variables for further univariate analysis. Of all categoric variables, loss of consciousness, cardiac arrest, hemoglobin <9 g/dl, blood pressure (BP) <90 mmHg and GCS <15 were associated with perioperative death. However, loss of consciousness and cardiac arrest were observed in only eight and five patients, respectively.

On logistic regression analysis of these five variables, none reach significance at the 5% level. Exclusion of the variables loss of consciousness and cardiac arrest yields the multivariate model seen in Table 3. The remaining variables were retained to determine the cumulative effect of multiple risk factors in a scoring system. With risk factors equally weighted, three probands of risk were established (Table 4). There was a significant association between actual mortality and cumulative risk factors ($p = 0.003$).

'able 1 Univariate analysis of reoperative continuous ariables in 105 patients

Variable	No. of missing cases	Survivors	Nonsurvivors	*p*
Age (years)		71.9 (7.4)	73.6 (6.7)	0.250
Duration of symptoms (hr)	6	6 (0–240)	4 (1–72)	0.218
Hemoglobin (g/dl)	1	12.0 (2.5)	10.7 (3.1)	0.038
WBC count ($\times 10^9$/L)	1	13.8 (6.5–33.7)	13.8 (5.2–31.1)	0.989
Platelets ($\times 10^9$/L)	3	195 (90–569)	207 (71–522)	0.353
Prothrombin time (s)	23	10 (8–31)	11 (9–62)	0.256
APTT (s)	25	32 (24–52)	32 (24–210)	0.206
Fibrinogen (g/L)	25	3.5 (1.5)	3.2 (1.5)	0.386
Urea (mmol/L)	1	7.6 (3.2–10.3)	7.0 (3.2–13.7)	0.688
Creatinine (μmol/L)	1	124 (78–498)	141 (84–263)	0.169
Albumin (g/L)	20	36 (19–51)	35 (17–45)	0.118
Sodium (mmol/L)	1	138 (124–148)	139 (122–148)	0.089
Potassium (mmol/L)	1	4.0 (0.7)	4.0 (0.5)	0.996
Alanine transaminase (U/L)	20	14 (6–221)	12 (5–154)	0.205
Highest pulse rate (bpm)	9	95 (55–190)	99 (60–130)	0.794
Lowest BP (mmHg)	5	80 (50–165)	73 (0–135)	0.003
Highest BP (mmHg)	10	150 (33)	135 (36)	0.049

'BC: white blood cells; APTT: tivated partial thromboplastin ne; BP: blood pressure

esults are the mean or the ean and range

able 2 Univariate analysis of reoperative categoric variables ı 105 patients

Variable	No. of missing cases	No. of observations		*p*
		Survivors	Nonsurvivors)	
Age ≥ 75 years		24	20	0.196
Female sex		8	5	1.000†
Interhospital transfer		28	19	0.672
Loss of consciousness	6	2	6	0.022†
Cardiac arrest		0	5	0.006†
ECG ischemia	7	22	16	0.313
Hb <9 g/dl	1	7	11	0.038
Creatinine >190 μmol /L	1	8	3	0.742
BP <90 mmHg	5	33	29	0.036
GCS <15	5	14	17	0.016
Diabetes	5	4	0	0.310†
Cardiac symptoms	6	24	12	0.921
Respiratory symptoms	4	30	17	1.000†
PAOD		4	7	0.095†
Previous vascular intervention		0	1	0.371†
Warfarin therapy		0	2	0.136†
β-Blocker therapy		19	8	0.480
Steroid therapy		2	1	1.000†
Antiplatelet therapy		32	15	0.710
Antianginal therapy		10	3	0.363†
Preoperative inotropes		1	3	0.143†

Hb: hemoglobin; GCS: Glasgow Coma Scale; PAOD: peripheral arterial occlusive disease

† Fisher's exact test

Discussion

Many authors have attempted to identify preoperative variables that predict outcome and that might define the group of patients at extreme risk who would not benefit from operation after AAA rupture. However, there has been little consistency in reported findings and poor reproducibility among differing patient populations. Furthermore, data from the authors' center have shown that two well established scoring systems, the Hardman Index

Table 3 Multivariate model of variables related to perioperative death

Variable	*p*	Odds ratio	95% CI
Hemoglobin <9 g/dl	0.102	2.519	0.831–7.630
BP <90 mmHg	0.148	2.020	0.779–5.241
GCS <15	0.077	2.318	0.916–5.866

CI: confidence interval

Table 4 Mortality of patients with three equally weighted risk factors[a] according to number of factors present.

No. of variables	No. of patients	No. of deaths	% Mortality
1	70	20	29
	30	15	50
	5	4	80

[a] Hemoglobin <9 g/dl, BP <90 mmHg, GCS <15

and the Glasgow Aneurysm Score—widely held to be credible instruments in risk prediction—lack validity [9]. Reasons for the poor performance of the present data, when applied to existing scoring models, are manifold. In contrast to much of the existing data, the present series represents a large number of patients accumulated over a short contemporary study period and operated on exclusively by a small group of specialist vascular surgeons. This is likely to minimize some of the bias associated with other retrospective analyses.

These data come from a high-volume tertiary unit serving a Scottish population of approximately 1.2 million individuals. Scoring systems always reflect the specific population and study period from which they were designed and modeled. For this reason, although a scoring system may hold true for one population, it must not be assumed to do so for other populations without appropriate, ongoing validation [14]. Although it may be argued that the current data are vulnerable to selection bias, as some patients were palliated and not subjected to attempted operation, there is no other ruptured AAA risk scoring system that has been modeled on patients treated by a specialist vascular service during the last decade.

Of the well known predictive instruments for ruptured AAA, all include age as a risk factor. In contrast, age was not found to be a significant risk factor in the present series. Age may be considered an indirect marker of physiologic status, and based on these data it seems to lack sensitivity as a predictor of adverse outcome. However, it is also surprising that renal function, as represented by the serum creatinine level, was not identified as a predictive variable when it too is included in both the Hardman and Glasgow scores. Preoperative creatinine >130 μmol/L is recognized as a perioperative risk factor for adverse outcome in noncardiac surgery [15]. However, the overall median (range) creatinine level in the current series was 129 μmol/L (78–498) μmol /L. This may imply that most patients with ruptured AAA had evidence of preoperative renal dysfunction and so creatinine might lack predictive value in this circumstance. Review of the existing literature reveals much conflicting data, and there is no consensus on the usefulness of creatinine as a risk factor for perioperative death.

Based on the present data, the goal of a scoring system that can accurately predict all patients in whom attempted repair will prove futile seems unrealistic. However, five significant risk factors were identified on univariate analysis. They all failed to retain significance at the 5% level when subjected to multivariate modeling. Of the five factors, in-hospital loss of consciousness and cardiac arrest are not useful predictive variables for patient stratification because of their low observed frequency. The two were only observed in eight and five patients, respectively, and are vulnerable to a type I error. Preoperative loss of consciousness was associated with death in six of the eight patients, and cardiac arrest was invariably associated with death, a naturally intuitive finding. However, previous work has shown that unconsciousness and arrest are not always fatal after aneurysm rupture [16, 17]. Although they have been frequently cited as useful risk factors for predicting death after ruptured AAA, and one is a component of the Hardman Index, it is unlikely that there is any single preoperative variable that in isolation can predict an unsuccessful outcome across different patient populations.

The remaining three variables noted on univariate analysis were retained for analysis in a multivariate model. Although they all lose significance at the 5% level, there is a trend to significance at an α level of 10%. The variables of hemoglobin <9 g/dl, shock (BP <90 mmHg), and GCS <15 are sensitive markers of the physiologic condition—hemoglobin level and blood pressure being directly proportional to tissue oxygen delivery, and GCS an indicator of adequate cerebral perfusion. All three variables have odd ratios of approximately two. When applied to an equally weighted, cumulative model of risk scoring, there are three clearly identifiable tiers of risk. Although even the most extreme band of risk is still associated with a 20% chance of survival, the instrument provides a useful method of assigning patients to a low-, medium-, or high-risk category prior to attempted operation. Furthermore, all three variables in the proposed model can be measured within a few minutes of a patient's arrival in the emergency department. The risk score can then be used to inform patients and relatives objectively of the illness severity and operative risk.

These data represent a novel, unvalidated predictive risk model for patients with ruptured AAA from a single UK

:rtiary center. The limitations of these data are that they 'e highly selected in that the patients at most extreme risk 'ere palliated and are not included in the analysis of ıriables predictive of perioperative death. However, such as is unavoidable in a study of this nature, particularly here a selective policy of surgical intervention is nployed. Although this instrument cannot be recom-ıended for use in patient selection at present, its potential .ility in comparative audit and supporting clinical judg-ıent warrants further prospective validation.

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Prediction of outcome after abdominal aortic aneurysm rupture

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Background: **Most vascular surgeons practice a selective policy of operative intervention for patients with ruptured abdominal aortic aneurysm (AAA). The evidence on which to justify operative selection remains uncertain. This review examines the prediction of outcome after attempted open repair of ruptured AAA.**
Methods: **The Medline and EMBASE databases and Cochrane Database of Systematic Reviews were searched for clinical studies relating to the prediction of outcome after ruptured AAA. Reference lists of relevant articles were also reviewed.**
Results: **The last 20 years has seen >60 publications considering variables predictive of outcome after AAA rupture. Four predictive scoring systems are reported: Hardman Index, Glasgow Aneurysm Score, Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity (POSSUM), and the Vancouver Scoring System. No scoring system has been shown to have consistent or absolute validity. Of the remaining data, there are no individual or combination of variables that can accurately and consistently predict outcome.**
Conclusions: **Little robust evidence is available on which to base preoperative outcome prediction in patients with ruptured AAA. Experienced clinical judgement will remain of foremost importance in the selection of patients for ruptured AAA repair. (J Vasc Surg 2008;47:222-30.)**

Most surgeons practice a selective policy of operative intervention for patients with ruptured abdominal aortic aneurysm (AAA).[1] This approach is underpinned by the rapid assessment of the patient's current clinical condition, premorbid health, and functional status to determine if attempted operation is appropriate and associated with a realistic chance of survival. It aims to ensure health care resources are used appropriately and avoid futile attempts at intervention in patients with prohibitive risk. In clinical practice, this patient selection is largely based upon subjective criteria. However, to ensure that selection is objective, a system that can accurately predict outcome in patients with ruptured AAA is crucial.

Many authors have attempted to identify variables capable of predicting death in patients with ruptured AAA. There is much heterogeneity in the nature and quality of results and the methods used for reporting. A few series have gone further and have performed statistical modelling on predictive variables to design scoring systems that can forecast outcome. In many systems, however, sound methodology has not been used in the design; furthermore, only a few have undergone robust audit, let alone prospective validation. A previous review has recognized that these limitations would render meta-analytical techniques unsuitable.[2] The following systematic review considers existing scoring systems and existing literature on variables predictive of outcome in patients with ruptured AAA.

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Competition of interest: none.
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METHOD

The Medline, EMBASE, and Cochrane Systematic Reviews (January 1985 to June 2006) electronic databases were searched. The search strategy used the MeSH headings "Aortic aneurysm, abdominal" and "aortic rupture or rupture.mp," with the Boolean operator "and." The OVID search engine 10.3.2 (Ovid Technologies, New York, NY) was used. Criteria for inclusion were studies assessing variables predictive of outcome in patients before attempted open repair of ruptured AAA. Studies that examined outcome in a subgroup of patients alone and those that only assessed selected variables were excluded. Manual searching was also done of reference lists from articles retrieved by electronic searching. Articles retrieved were restricted to those published in English. All identified articles were obtained through local library collections and The British Library.

RESULTS

Hardman index. The Hardman scoring system is probably the most well known of scoring systems for use in patients with ruptured AAA. Originally described in 1996, this retrospective series reviewed 154 nonconsecutive patients who underwent operation for ruptured AAA between 1985 and 1993 at a single Australian tertiary vascular center.[3] Univariate analysis was done on 67 preoperative variables in 136 patients for their association with death in-hospital or ≤30 days of surgery. Continuous variables significantly associated with death were categorized into quartiles, and the mortality rate of each category examined. All variables related to postoperative death were further analyzed alongside data from another 18 patients to develop a multivariate model. The significant multivariate risk factors were then assessed for their cumulative effect when weighted equally.

Table I. Operative mortality (%) according to number of Hardman variables

First author	*Year*	*Patients, No.*	*No. of Hardman variables*			
			0	*1*	*2*	*≥3*
Hardman[3]	1996	154	16%	37%	72%	100%
Prance[4]	1999	69	18%	28%	48%	100%
Neary[5]	2003	188	35%	55%	74%	90%
Boyle[6]	2003	79	8%	24%	55%	100%
Calderwood[7]	2004	137	40%	46%	77%	92%*
Tambyraja[8]	2005	85	15%	55%	38%	33%

*Mortality for 3 risk factors only. For 4 risk factors, mortality was 100%.

Five independent variables were identified on multivariate analysis: preoperative hemoglobin level <9 g/L, serum creatinine level >90 μmol/L, electrocardiographic ischemia, in-hospital loss of consciousness, and age >76 years. No single risk factor had a predictive value in isolation, but the cumulative predictive value of the risk factors is summarized in Table I. Three or more of the five risk factors were associated with a 100% mortality rate.

After its conception, the Hardman score was commended for its simplicity and practicality in the acute setting. Validation of the system has been performed at various levels. To date, six studies have assessed the performance of the Hardman system.[4-8] These are summarized in Table I.

On initial inspection, these results seem to support the original data of Hardman and colleagues. Of the five series, three or more positive variables are uniformly associated with perioperative death in three studies. However, it is concerning that three of the reports contain patients with three or more variables who survived operative repair. Although it has been widely concluded that the presence of more than three Hardman variables is a good predictor of death, this would seem not to be universally true.

More critical analysis of these data reveals that all but one review is retrospective in nature and the only prospective data are compiled from two centers. These data add some credence to the validity of the Hardman score system but also highlight that the instrument is not as precise as initially reported. This emphasizes the need for further prospective validation before its use in clinical practice can be unanimously supported.

Glasgow aneurysm score. The Glasgow Aneurysm Score (GAS) was first reported in 1994.[9] This instrument was originally developed as a tool for prognostic scoring in patients undergoing repair of intact or ruptured AAA. A retrospective, multicentered, nonconsecutive sample of 500 patients undergoing AAA repair at general surgical units in Glasgow between 1980 and 1990 was examined for risk factors associated with death. Multivariate analysis identified the independent risk factors of age, shock, myocardial disease, cerebrovascular disease, and renal disease. Myocardial disease is typified by documented myocardial infarction or on-going angina, or both. Cerebrovascular disease refers to all grade of stroke, including transient ischemic attacks. Renal disease is any combination of history of chronic or acute renal failure, urea level >20 mmol/L, or creatinine level >150 μmol/L at presentation.

Rounding of the regression coefficients created a simple risk score: risk score = age in years + 17 (for shock) + 7 (for myocardial disease) + 10 (for cerebrovascular disease) + 14 (for renal disease). Appraisal of the scoring system showed that mortality rate increased in proportion to score. The same authors prospectively evaluated their system in a subsequent multicentered study.[10] Again, they reported similar results to the original analysis used in developing the score. Mortality was found to correlate well with GAS, and scores of >95 were related to a mortality rate of >80%.

This generic scoring system for patients undergoing AAA repair has had little further validation. Given its simplicity, ease of use, and apparent predictive power, this seems surprising. However, a Finnish group recently examined the performance of the GAS in a retrospective review of 836 patients with ruptured AAA admitted to 21 hospitals and included in a large national vascular registry.[11] These data confirmed that the GAS was independently associated with postoperative death. This series did not have a cutoff score that predicted a postoperative mortality rate of 100%, although a score of >98 was associated with a mortality rate of about 80%.

We have previously reported the results of our own retrospective audit of the GAS.[8] A surprising finding was that the GAS performed poorly as a predictive tool. Indeed, it was impossible to identify any score that conferred extreme risk, and even in 14 patients with scores of ≥110, operative mortality was <50%. Despite its apparent merits, further attempts at validation have yielded conflicting results. Until further data are available, its use in outcome prediction and as a risk-stratification tool for comparative audit must be questioned.

The physiological and operative severity score for the enumeration of mortality and morbidity. The POSSUM score was described and prospectively validated by Copeland et al[12] in 1991. Its primary function was as a scoring system for general surgical audit to allow for the effects of case-mix rather than as an instrument to predict individual case outcome. POSSUM represents a risk-prediction model based on a physiology score derived from 12 preoperative variables, which are independently predictive of adverse postoperative outcome on multivariate analysis,

Table II. Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity (POSSUM) physiologic and operative variables

Physiological score	*Operative score*
Age, y	Operation category (minor, intermediate, major, major+)
Cardiac signs	No. of procedures
Respiratory signs	Total blood loss, mL
Systolic blood pressure, mm Hg	Peritoneal soiling
Pulse rate, per min	Malignancy
Glasgow Coma Score	Timing of operation
Serum urea, mmol/L	
Serum sodium, mmol/L	
Serum potassium, mmol/L	
Hemoglobin, g/L	
White cell count, $\times 10^9$/L	
Electrocardiogram	

Mortality risk equations (R = risk of mortality):
POSSUM: $\ln (R/1-R) = -7.04 + (0.13 \times$ physiological score$) + (0.16 \times$ operative severity score).
Vascular (V)-POSSUM: $\ln (R/1-R) = -8.0616 + (0.1552 \times$ physiological score$) + (0.1238 \times$ operative severity score).
V-POSSUM (physiological score only): $\ln (R/1-R) = -6.0386 + (0.1539 \times$ physiological score).
Ruptured abdominal aortic aneurysm (RAAA)-POSSUM: $\ln (R/1-R) = -4.9795 + (0.0913 \times$ physiological score$) + (0.0958 \times$ operative severity score).
RAAA-POSSUM (physiological score only): $\ln (R/1-R) = -2.7569 + (0.0968 \times$ physiological score).

and an operative score derived from six further intraoperative variables (Table II). Each of the variables is graded and scored exponentially as 1, 2, 4, or 8.

The combined physiology and operative scores were subjected to logistic regression analysis to generate risk equations that convert the scores into a predicted percentage morbidity and mortality. However, attempted validation in both general and subspecialty surgery has reported a lack of calibration of the initial model and suggestions for remodelling of the regression equation have been proposed.[13-16] This led to the Vascular Surgical Society of Great Britain and Ireland developing a risk equation specific for patients undergoing vascular surgery, the V-POSSUM.[17] Specific evaluation of the POSSUM system in ruptured AAA repair demonstrated that the equation performed poorly in emergency aortic surgery.[18]

Subsequently, two further equations exclusively for ruptured AAA were derived from a retrospective series of 106 patients.[19] One equation incorporated both physiology and operative scores and the other only used the physiology score. Initial validation was performed by the authors on a further set of 107 patients with ruptured AAA. The physiology-only equation was effective but was found to have a lack of fit at a certain risk range. However, the ruptured AAA POSSUM (RAAA-POSSUM) equation that combined physiology and operative scores was more successful at accurately predicting outcome.

Two further series have examined the validity of both RAAA-POSSUM systems. Both equations were used to analyze retrospective data on 188 patients with ruptured AAA from Gloucester.[5] Both systems performed well, with no difference in observed and expected mortality results. A further nonconsecutive, retrospective series of 68 patients who survived >24 hours after repair of a ruptured AAA from Leicester also confirmed that although the two systems tended to slightly overpredict death, there was no statistically significant lack of fit. However, the limitations of the latter highly selected data set are obvious.[20]

To date, the RAAA-POSSUM systems have not been prospectively validated. Although the existing evidence suggests that they perform well, the utility of the POSSUM system in clinical decision making is questionable. It is paramount to reiterate that the POSSUM methodology is principally for comparative audit. The need for operative variables renders most POSSUM equations impractical for preoperative risk prediction.

Although the data required for the physiology RAAA-POSSUM tool are easily recorded, the need for complex mathematical equations can make its utility cumbersome in the clinical setting. The system allows for more precise risk stratification of patients than some of the other systems already described. This level of accuracy may introduce even more complexity to clinical decision making. In the Gloucester study, one of 16 patients with a predicted mortality risk of >80% survived, as did three of 21 with a risk of 70% to 80%. Using this system, the absolute prediction of operative futility would appear unfeasible.

Vancouver scoring system. Of scoring systems applicable to patients with ruptured AAA, the Vancouver system is probably the least well known and used.[21] Also reported in 1996, this retrospective series examined 147 patients who underwent repair of a ruptured AAA between 1984 and 1993. Perioperative demographic and physiologic variables significantly associated with death on univariate analysis underwent further multivariate analysis.

Univariate analysis identified age, reduced conscious level, preoperative cardiac arrest, history of myocardial infarction, and a history of collapse as being associated with postoperative death. After multivariate logistic regression analysis, age, reduced conscious level, and preoperative cardiac arrest remained as significant predictors of death. These variables could be entered into a predictive model equation on the basis of the coefficients from the logistic regression model. The probability of death is estimated using the equation $[e^x/(1 + e^x)]$, where e is the base of the natural logarithm and x is the constant (-3.44) + sum of coefficients for the significant variables (Table III).

The Vancouver group has also attempted to validate their statistical model. They evaluated the performance of the instrument on a prospective series of 134 patients drawn from two tertiary centers.[22] The authors argue that their system is accurate at predicting patients at extreme risk (patients with a predicted mortality >90%); however, the instrument seems to perform less well at lower levels of mortality risk (patients with a predicted mortality >80%). The group concluded that their tool was of use in informing clinical decisions in patients with ruptured AAA, although unable to identify a 100% mortality rate.

Table III. Risk factor coefficients from the Vancouver scoring system

Variable	*Category*	*Coefficient (Constant = −3.41)*
Age		0.062 × age
Loss of consciousness	Yes	1.14
	No	−1.14
Cardiac arrest	Yes	0.60
	No	−0.60

Table IV. Series failing to identify variables predictive of death after operation

First author	*Year*	*Patients, No.*	*Deaths, %*
Campbell [23]	1986	52	56
Vohra [24]	1988	92	39
Harris [25]	1991	113	64
Meesters [26]	1994	99	49
Barry [27]	1997	140	52
Hatori [28]	2000	33	39
Bown [20]	2003	139*	32
Sultan [29]	2004	42	60

*Excludes patients who died ≤24 hours of operation.

Despite their assertion, this scoring system does not seem to have gained support and been used by other centers. No further independent validation is identifiable in the literature. Reasons for this may be related to the nature of the model. Although the variables used are easily obtained, the need for coefficients and complex mathematical formula render it less practicable in the acute situation. The derivation of a percentage risk of death is similar to the GAS and POSSUM systems. This instrument may have a utility for risk stratification for the purposes of audit, although more robust validation is needed to assess its credentials. Its use in clinical decision making in the acute setting is hampered by its complexity.

Other predictive variables. Interest in the prediction of clinical outcome in patients with AAA rupture is highlighted by the publication of >60 independent series investigating the subject in the last 20 years alone. Although the preceding scoring systems are, perhaps, the most sophisticated and well cited of these articles, the others also offer potentially useful data to inform clinical judgement.

Eight of these further articles reported negative results and were unable to identify any preoperative variables predictive of death after aneurysm rupture (Table IV).[20,23-29] These studies on 710 patients from European and North American centers are all retrospective in design. The median sample size was 92 (range, 33 to 140) and mortality was 49% (range, 32% to 64%). These data provide compelling evidence for the argument that absolute prediction of outcome in this disease is impossible. It is argued that withholding an operation on the basis of any predictive variables is unsound and ethically unjustified.[25] Some of the most highly regarded authorities in vascular surgery have championed this thesis.[30] It may also be assumed that an even greater body of similar unpublished data exists owing to the nature of publication bias.

Examination of the available data generates some concerns, however. Of the three series that study >100 patients, one excluded patients who died ≤24 hours of operation,[20] and another shared a data set with a further publication that a year later reported female gender, preoperative hypotension, low hemoglobin level, and thrombocytopenia as predictors of death.[27] Critics also have questioned whether "cardiac arrest" in these series simply represented an inability to palpate pulses due to hypotension or arrhythmia rather than true loss of cardiac output. Nevertheless, irrespective of these deficiencies, such data cannot be ignored.

The remaining 55 series all describe one or more preoperative variables that were predictive of outcome in 81,350 patients (Table V).[31-80] It must be noted that two series have similar characteristics and are likely to represent duplicate publication of an extended data set.[77,80] The median number of patients studied was 119 (range, 18 to 67,751), and median mortality was 47% (range, 13% to 75%). It is noteworthy that only two studies were prospective in design.[48,56] Most data have been subjected to multivariate statistical tests, where appropriate, although some large series have only undertaken univariate analysis. Apart from the Hardman data, no other group has robustly identified preoperative variables, individually or combined, that are capable of defining a group with such a prohibitive risk of death that intervention is precluded. Even patients with preoperative cardiac arrest, a group that is intuitively at an extreme risk of mortality, are reported to have survival rates of up to 33% in certain series.[59]

Nevertheless, 10 variables regularly appear as significant predictors of death. If one takes hematocrit and serum hemoglobin as analogous variables, six of these appear more frequently than others. These six include hypotension, advanced age, cardiac arrest, raised serum creatinine level, low hemoglobin/hematocrit, and a history of ischemic heart disease. Of interest is that these variables or their correlates are all represented in the established scoring systems described earlier.

The risk factors of hypotension, cardiac arrest, raised creatinine level, low hemoglobin level, loss of consciousness, and electrocardiographic ischemia have retained independent statistical significance on multivariate analysis, and they are all implicated in the development or a manifestation of systemic shock. Furthermore, more than half of these 54 publications identify hypotension as a predictor of mortality. Of the reported risk factors, female gender is, perhaps, the most difficult to interpret. Four of the five data sets that describe this finding are North American and have considerable sample sizes. The over-representation of women in elective and emergency AAA mortality statistics is well described, but the reasoning remains uncertain.[81]

Table V. Series identifying preoperative variables predictive for death after attempted repair of ruptured abdominal aortic aneurysm

First author	*Year*	*Patients, No.*	*Deaths, %*	*BP, mm Hg*	*Age, y*	*Cardiac arrest*	*Creatinine, μmol/l*
Donaldson[31]	1985	81	43		•(>76)*		
Lambert[32]	1986	180	75	•(<80)			
Morishita[33]	1986	20	45	•*			
Nachbur[34]	1987	116	47		•*		
Shackleton[35]	1987	106	40				
Martin[36]	1988	58	26	•(<90)			
Amundsen[37]	1989	103	59	•(<92)	•(>71)		
Ouriel[38]	1990	243	55	•(<70)			•(>300)
Murphy[39]	1990	172	49	•(<90)*		•*	
Johansen[40]	1991	186	70		•(>80)*	•*	
AbuRahma[41]	1991	73	62	•(<90)			
Gloviczki[42]	1992	231	42	•			
Rosenthal[43]	1992	47	43	•(<90)*	•(>75)*	•*	
Scott[44]	1992	66	30		•‡		
Bauer[45]	1993	314	29	•(<90)			
McCready[46]	1993	208	50	•(<90)	•(>70)		
Katz[47]	1994	99	57		•		
Johnston[48]	1994†	147	49				•(>130)
Katz[49]	1994	1829	50	•			
Panneton[50]	1995	112	49	•(<90)		•	
Browning[51]	1995	54	44	•(<85)			
Marty-Ane[52]	1995	61	13		•		
Farooq[53]	1996	122	56	•(<80)		•	
Jaakkola[54]	1996	48	65	•(<90)			
Rutledge[55]	1996	1480	54		•*		
Chen[21]	1996	157	46		•	•	
Hardman[3]	1996	154	39		•(>76)		•(>190)
Koskas[56]	1997†	158	47	•	•		•
Martinez[57]	1997	84	57	•(<90)	•		
Lazarides[18]	1997	40	55				
Halpern[58]	1997	96	60	•(<90)			•(>150)
Satta[59]	1997	51	47	•*			
Subramaniam[60]	1998	18*	67	•*			
Barry[61]	1998	150	48	•*			
Dardik[62]	1998	527	47		•		
Van Dongen[63]	1998	309	25		•(>70)		
Sasaki[64]	1998	27	22	•(<80)	•		
Urwin[65]	1999	135*	63		•	•	
Ho[66]	1999	40	48		•		
Kniemeyer[67]	2000	57	32	•(<80)			
Turton[68]	2000	102	53	•(≤90)		•	
Heller[69]	2000	67751	46		•(>70)		•
Lovricevic[70]	2000	54	30	•‡		•‡	
Merlo[71]	2001	123	45		•*		
Noel[72]	2001	413	37			•	
Alonso-Perez[73]	2001	144	47	•(<80)	•		
Gutierrez-Morlote[74]	2002	106	49	•(<90)			
Hans[75]	2003	101	48		•		
Piper[76]	2003	147	35				
Markovic[77]	2004	229	54	•(<95)*		•*	•(>180)*
Lo[78]	2004	41	41				•
Dueck[79]	2004	2601	41		•		
Calderwood [7]	2004	137	56	•(<100)	•(>76)		•(>190)
Korhonen[11]	2004	836	47	•			
Davidovic[80]	2005	406	48	•*		•*	•(>180)*

LOC, Loss of consciousness; IHD, ischemic heart disease; *BP*, blood pressure; *Hb*, hemoglobin; *Het*, hematocrit; *APACHE II*, Acute Physiology and Chronic Health Evaluation II; *TIA*, transient ischemic attack; *AAA*, abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease.

•This variable was predictive of death.

*Univariate analysis only.

†Prospective studies.

‡No statistical analysis.

Table V. Continued

Hb, g/L)	*Hct, %*	*IHD*	*LOC*	*Sex (M/F)*	*ECG changes*	*Platelets ($\times 10^9$/l)*	*Other*
	•(<30)*				•**		
		•					Hypertension
							Duration of symptoms,* associated disease,* duration of AAA
			•				Duration of symptoms <6 h*
							Cardiac failure, anion gap
							Collapse*
				•(F)*			
	•						Collapse
							APACHE II score
							Treatment delay*
		•					
	•						
				•(F)			Chronic renal failure
		•					
		•					
				•(F)*			
			•				
•(<9)			•		•		
							Stroke/TIA
						•	
•(<10)			•				
•*							
•(<10)*							COPD*
•*				•(F)*		•*	
		•					COPD
•(<9)					•	•(<100)	
				•(F)			Afro-Caribbean race
			•‡				
						•(<100)*	Hypertension*
	•						APACHE II
					•		
	•(<35)						Treatment delay
							Core temp
•(<10)*	•(<29)*	•*	•*				Low urine output,* leucocytes >14×10^9 /L,* urea >11 mmol/L*
				•(F)			
					•		
•(<10)*	•(<29)*		•*				Low urine output*, Leucocytes > 14 ×10^9/ L,* urea >11 mmol/L*

DISCUSSION

The existing literature suggests that certain patient-related preoperative variables are associated with perioperative death after AAA rupture. Of note, however is that surgeon- and hospital-related variables are also known to have a profound impact on outcome.[79] Recent data have confirmed that outcome in terms of death after ruptured AAA repair is better in high-volume centers.[82] This factor may be implicated in the poor comparative performance of existing scoring systems that were derived from low-volume or non-specialist institutions. With the introduction of endovascular repair of ruptured AAA and the potential improvements in patient survival, risk scoring instruments may require further remodelling or recalibration.[83,84]

Predictive scoring systems are derived from a combination of demographic, physiologic, and therapeutic variables. It is ideal to try to generate the most accurate value of risk scoring from the least number of predictors by excluding variables that do not influence outcome. The selection of these variables is performed by a combination of statistical modelling and expert opinion. After an analysis on a development data set, validation should be performed on a separate data set from the same institution before being applied to data from other centers and compared with the performance of other predictive tools.[85]

There is much to be desired in terms of the quality and level of available evidence. In the past 20 years, no more than two prospective attempts to investigate risk factors associated with death after AAA rupture have been published. Furthermore, the measure and reporting of significant perioperative morbidity in this group of patients continues to lack accuracy and focus.[86]

CONCLUSION

At present, no scoring system or variable, in combination or on its own, can be persuasively recommended as being predictive of perioperative death and be used to influence treatment decisions. The existing scoring systems have not been adequately validated to be of use in dictating therapy or justifying clinical decision making. At best, they are useful to risk stratify patients for the purposes of audit and act as an adjunct to supplement clinical intuition. Until a scoring system that uses sound methodology and robust validation is available, experienced clinical judgement will remain of foremost importance in the selection of patients for ruptured AAA repair.

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Prognostic scoring in ruptured abdominal aortic aneurysm: A prospective evaluation

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Background: **Prospective validation of prognostic scoring systems for ruptured abdominal aortic aneurysm (AAA) is lacking. This study assesses the validity of three established risk scores and a new prognostic index.**

Method: **Patients admitted with ruptured AAA during a 26-month period (August 2002-December 2004) were recruited prospectively. The Glasgow Aneurysm Score (GAS), Hardman Index, Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity (POSSUM) scores, and the Edinburgh Ruptured Aneurysm Score (ERAS) were recorded and related to outcome.**

Results: **During the study period, 111 patients were admitted with ruptured AAA. Of these, 84 (76%) underwent attempted operative repair and were included in the study; 37 (44%) died after operation. The GAS, Hardman Index, and the ERAS were statistically related to mortality. However, analysis by receiver-operator characteristic curve revealed the ERAS to have an area under the curve (AUC) of 0.72 (95% confidence interval [CI], 0.61-0.83). The vascular (V)-POSSUM and ruptured AAA (RAAA)-POSSUM models had an AUC of 0.70 (95% CI, 0.59-0.82). The Hardman Index and GAS had an AUC of 0.69 (95% CI, 0.57-0.80) and 0.64 (95% CI, 0.52-0.76), respectively. Although the V-POSSUM equation predicted mortality effectively (P = .086), the RAAA-POSSUM derivative demonstrated a significant lack of fit (P = .009).**

Conclusion: **Prospective validation shows that the Hardman Index, GAS, and V-POSSUM and RAAA-POSSUM scores do not perform well as predictors for death after ruptured AAA. The ERAS accurately stratifies perioperative risk but requires further validation. (J Vasc Surg 2008;47:282-6.)**

The incidence of patients presenting with ruptured abdominal aortic aneurysm (AAA) is increasing.[1,2] To ensure appropriate use of health care resources and avoid futile attempts at intervention in patients with prohibitive risk, judicious patient selection is essential. Upon presentation, the patient's clinical condition must be rapidly assessed to determine if attempted operation is appropriate and associated with a reasonable chance of survival. For the most part, this is largely a subjective decision; however, a scoring system that could accurately predict outcome in patients before operation would allow selection to be objective and more easily justified. Appropriate risk stratification of patients would also support comparative audit within and between institutions.

The Glasgow Aneurysm Score (GAS), Hardman Index, and Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) risk equations are predictive scoring systems recommended for use in patients with ruptured AAA.[3-5] Recently, our center has developed the Edinburgh Ruptured Aneurysm Score (ERAS), a further novel prognostic index that, in contrast to other scores, was derived from a contemporary data set.[6] However, none of these scoring systems have been adequately validated to be of use in dictating therapy or justifying clinical decision making. This prospective study examined preoperative variables predictive of death after AAA rupture and assessed the validity of existing scoring systems.

METHOD

Local Research Ethics Committee approval was obtained for this prospective study. All patients admitted to the Edinburgh Vascular Surgical Service for repair of a ruptured AAA during a 2-year period (August 2002-December 2004) were included in this prospective study. Operation was defined as the delivery of an anesthetic with the intention of performing AAA repair. Ruptured AAA was defined as the presence of retroperitoneal or intraperitoneal blood, or both, in the absence of any other identifiable cause for hematoma other than an aneurysm.[7]

All patients were operated on by one of five consultant vascular surgeons. For each patient, 53 preoperative variables, identified in other studies or suspected on clinical grounds to be associated with mortality, the GAS, Hardman Index, V-POSSUM and ruptured AAA (RAAA)-POSSUM (physiology only) scores, and ERAS were recorded at the point of admission, before operation, and related to 30-day or in-hospital mortality. The protocols observed within our unit did not advocate the use of endovascular aortic repair for emergency AAA repair during the study period. Surgical intervention was generally not undertaken if the patient declined operation, had a known serious comorbidity such as advanced malignancy, or was

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Table I. POSSUM physiologic and operative variables

Physiologic	*Operative*
Age (years)	Operation category (minor, intermediate, major, major+)
Cardiac signs	Number of procedures
Respiratory signs	Total blood loss (mL)
Systolic blood pressure, mm Hg	Peritoneal soiling
Pulse rate/min	Malignancy
Glasgow Coma Score	Timing of operation
Serum urea, mmol/L	
Serum sodium, mmol/L	
Serum potassium, mmol/L	
Hemoglobin, g/L	
White cell count, $\times 10^9$/L	
Electrocardiogram	

POSSUM, Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity.
Mortality risk equations (*R* is the risk of mortality): V-POSSUM (Physiology score only): ln (R/1–R) = −6.0386 + (0.1539 × physiologic score). RAA-POSSUM (Physiology score only): ln (R/1–R) = −2.7569 + (0.0968 × physiologic score).

otherwise unsuitable, such as refractory loss of consciousness or cardiac arrest, severe dementia, or poor functional status.

The GAS is calculated using the following formula: risk score = age in years + 17 (for shock) + 7 (for myocardial disease) + 10 (for cerebrovascular disease) + 14 (for renal disease). Shock is defined on clinical grounds by tachycardia, hypotension, pallor, and sweating. Myocardial disease is previously documented myocardial infarction or ongoing angina, or both. Cerebrovascular disease refers to all grades of stroke, including transient ischemic attacks. Renal disease is any or all of a history of chronic or acute renal failure, urea level >20 mmol/L, or a creatinine level >150 μmol/L at presentation.[3]

The Hardman Index is derived from five preoperative variables: age >76 years, serum creatinine level >190 μmol/L, hemoglobin level <9 g/dL, myocardial ischemia on electrocardiograph, and a history of loss of consciousness after hospital arrival.[4] A patient may score between 0 (no Hardman variables present) and 5 (5 Hardman variables present). It has been reported that the presence of ≥3 variables is uniformly fatal.[8,9]

The POSSUM represents a risk-prediction model based on a physiology score derived from 12 preoperative variables, independently predictive of adverse postoperative outcome on multivariate analysis, and an operative score derived from six further intraoperative variables. To allow for preoperative risk scoring, the physiology score may be subjected to risk equations developed for vascular surgery (V-POSSUM) and ruptured AAA (RAAA-POSSUM) that convert the scores into a predicted percentage mortality (Table I).[5,10]

The ERAS derives from three preoperative variables: hemoglobin level <9 g/dL, a best-recorded in-hospital Glasgow Coma Scale of <15, and a recorded in-hospital blood pressure of <90 mm Hg. A patient may score ≤1, 2, or 3, depending on the number of variables present. These bands of risk correspond to a predicted mortality of 30%, 50%, and 80%, respectively.[6]

Table II. Primary reason for refusal of surgery in 27 patients

Reason for refusal	*Patients, No.*
Refractory cardiac arrest/LOC	13
Cardiorespiratory comorbidity	6
Age-related comorbidity	5
Patient wishes	2
Disseminated malignancy	1

LOC, Loss of consciousness.

Statistical analysis was performed using SPSS 13.0.0 software (SPSS Inc, Chicago, Ill). The receiver-operator characteristic (ROC) curve and χ^2 test for trend was used to compare the performance of the GAS, Hardman Index, POSSUM models, and ERAS in predicting postoperative death. The POSSUM-predicted mortality was evaluated by means of the χ^2 test, using the methods described by Hosmer and Lemeshow as appropriate,[11,12] and $P \leq .05$ was considered significant.

RESULTS

During the study period, 111 patients were admitted with ruptured AAA, and 27 (24%) were deemed unfit for aneurysm repair due to prohibitive comorbidity. There were 17 men and 10 women of a median (interquartile range) age of 79 (73-84) years. Reasons for nonoperative management are listed in Table II. Risk scores for the GAS, Hardman Index, V-POSSUM and RAAA-POSSUM mortality scores, and ERAS in the 11 patients who were turned down for surgery on the basis of comorbidity (apart from advanced malignancy) are summarized in Table III.

The remaining 84 patients underwent attempted repair of ruptured AAA and are included in the present analysis. There were 74 men and 10 women of a median (interquartile range) age of 73 (67-78) years. Thirty-seven patients (44%) died after operation, whereas of all patients admitted to hospital with a ruptured AAA during the study period, 63 (57%) died. One patient who did not undergo attempted repair survived her ruptured AAA and was discharged to a nursing home.

Glasgow Aneurysm Score. The mortality rates in terms of tertiles of GAS distribution are summarized in Table IV. The GAS was statistically related to death after attempted repair of ruptured AAA. The median (interquartile range) GAS was significantly greater in patients who survived operative repair than those who did not: 90 (82-106) vs 99 (91-112; $P = .027$). Analysis of the ROC curve showed that the GAS had an area under the curve (AUC) of 0.64 (95% confidence interval [CI], 0.52-0.76) for predicting perioperative death.

Hardman Index. The mortality rates in terms of Hardman Index distribution are summarized in Table V. There was a significant association between the Hardman

Table III. Risk scores in 11 patients who were palliated due to comorbidity

Patient	*Reason for palliation*	*Age*	*GAS*	*HI*	*V-POSSUM mortality, %*	*RAAA-POSSUM mortality, %*	*ERAS*
1	Cardiac dysfunction, suprarenal AAA	73	107	0	41	70	1
2	Cardiac dysfunction, suprarenal AAA	79	96	1	38	67	1
3	Cardiac dysfunction, chronic renal failure	83	121	3	88	91	2
4	Cardiac dysfunction	87	111	4	88	91	3
5	Cardiac dysfunction, chronic renal failure	89	120	3	57	77	2
6	Severe COPD	80	97	1	31	63	1
7	Previous disabling stroke	71	120	2	79	87	2
8	Pre-existing severe brain injury	76	100	1	31	63	2
9	Severe dementia	76	110	2	45	72	2
10	Extreme age	92	116	2	71	83	3
11	Extreme age	92	119	1	15	49	2

AAA, Abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease; *ERAS*, Edinburgh Ruptured Aneurysm Score; *GAS*, Glasgow Aneurysm Score; *HI*, Hardman Index; *POSSUM*, Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity; *V*, vascular; *RAAA*, ruptured abdominal aortic aneurysm.

Table IV. Distribution and mortality rates in 84 patients according to tertiles of Glasgow Aneurysm Score

Glasgow Aneurysm Score	*<89*	*89-105*	*>105*
Patients, No. (%)	28 (33)	28 (33)	28 (33)
Deaths, No (%)	8 (29)	13 (46)	16 (57)

Table V. Distribution and mortality rates in 84 patients according to the Hardman Index

Hardman Index	*0*	*1*	*2*	*≥3*
Patients, No. (%)	21 (25)	34 (40)	18 (21)	11 (13)
Deaths, No. (%)	6 (29)	11 (32)	12 (67)	8 (73)

score and operative death ($P = .010$). Analysis of the ROC curve showed that the Hardman score had an AUC of 0.69 (95% CI, 0.57-0.80) for predicting perioperative death.

Edinburgh Ruptured Aneurysm Score. There was a significant association between ERAS score and operative death ($P < .001$; Table VI). Analysis of the ROC curve showed that the ERAS had the largest AUC of 0.72 (95% CI, 0.61-0.83) for predicting perioperative death.

Possum. The ROC curve analysis showed that the POSSUM models had an AUC of 0.70 (95% CI, 0.59-0.82) for predicting perioperative death. Table VII summarizes the predicted risk of death and observed mortality rate for each of the POSSUM models used. The V-POSSUM (physiology only) model did not demonstrate any lack of fit. However, the RAAA-POSSUM (physiology only) model demonstrated a significant lack of fit ($P = .009$).

DISCUSSION

Although there have been several attempts to devise a prognostic score with which to predict outcome in patients with ruptured AAA, few have undergone robust validation. The use of an imprecise predictive tool to justify clinical decision making is open to question.

Table VI. Distribution and mortality rates in 84 patients according to Edinburgh Ruptured Aneurysm Score

Edinburgh Ruptured Aneurysm Score	*≤1*	*2*	*3*
Patients, No. (%)	46 (55)	27 (32)	11 (13)
Deaths, No. (%)	12 (26)	16 (59)	9 (82)

Previous validation of the GAS has come from prospective data pooled from three Scottish centers, retrospective data from the multicenter Finnvasc database, retrospective data from a tertiary vascular center in Rome, and from our own institution.[13-16] Apart from the Edinburgh data, the other data sets commend the GAS for its predictive power and validity. Of interest is that the more recent data from Rome noted that no patient with a GAS of >100 survived, whereas the Finnish data describe a mortality rate of approximately 80% for patients with a score of >98.[15,16] Similarly, the original Glasgow authors reported that scores of >95 were associated with a mortality rate of 80%.[14]

The present prospective data contradict the findings of these three previous series. Although the GAS was statistically associated with death, the performance of the instrument is much less precise. Patients with scores of <90 are at low risk, but it appears difficult to identify the group of most interest: those patients at extreme risk. Potential reasons for the contrasting performance of the GAS when applied to our data have been described.[13] Most of the preceding data stem from low-volume institutions that operate on <20 patients with ruptured AAA each year. It seems likely that the relationship between hospital and surgeon volume and improved outcome is likely to be important.[17]

Ten series have examined the validity of the Hardman Index; only one has been prospective.[3,8,9,13,16,18-22] Initial reports and consensus was that the Hardman Index accurately predicted death after ruptured AAA. The presence of three or more variables was widely held to be fatal[8,9]; however, more recent data have shown that the instrument

Table VII. Predicted and observed mortality according to V-POSSUM (physiology only) and RAAA-POSSUM physiology only) models

	Predicted risk		*Mortality*			*Overall result for each model*	
	Range, %	*Mean, %*	*Range, No.*	*Predicted*	*Observed*	χ^2	χ^2 P
V-POSSUM							
	0-31	16	44	7	13	6.61	
	31-50	42	17	7	7	0.01	
	50-70	59	12	7	9	1.21	
	70-100	80	11	9	8	0.32	
	0-100	36	84	30	37		8.16 .086 (4df)
RAAA-POSSUM							
	0-55	41	31	13	9	1.91	
	55-70	63	23	15	8	8.13	
	70-80	75	15	11	9	1.73	
	80-100	86	15	13	11	1.86	
	0-100	61	84	51	37		13.63 .009 (4df)

POSSUM, Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity; *V,* vascular; *RAAA,* ruptured abdominal aortic aneurysm.

does not perform as well as initially reported.[13,19-22] The present prospective data confirm that the Hardman Index does not display as convincing validity as initially reported. Although increasing score is associated with death, its predictive ability is only moderate, and the Hardman Index does not clearly identify patients who are at extreme risk in whom attempted operation is futile. The merits of the present data are not only its prospective nature but also the fact that only one patient had an incomplete set of scoring data. In the existing literature, data have been unavailable for up to 42% of patients.[22] Indeed, in the only other reported prospective study, data were missing on almost a third of patients.[9]

The POSSUM score is a tool that was designed to support comparative audit. It is important to recognize that it has never been recommended for outcome prediction. No prospective validation of the POSSUM risk equations recommended for vascular surgery when applied to patients with ruptured AAA has been reported. Of the existing retrospective literature, both the RAAA-POSSUM and V-POSSUM equations were shown accurately to predict risk when applied to preoperative data on 191 patients from Gloucester.[18] From the present preoperative data, both equations perform less well, although only the RAAA-POSSUM model demonstrated a significant lack of fit. The RAAA-POSSUM model over-predicted risk, whereas the V-POSSUM model tended to under-predict at the lower bands of risk. This lack of fit raises concerns about its use as a risk-stratification tool for comparative audit of death from ruptured AAA. Reasons for the discrepancy are unclear, but further validation of this model is needed.

The ERAS was modelled on retrospective data from patients presenting to our institution with ruptured AAA during a 2-year period. It has had no internal or external validation and cannot be recommended for clinical use at present. When applied to the present data, the score was significantly associated with perioperative death. The appeal of this scoring system is its simplicity and the ease with which the three components of the score can be obtained and applied, and even the hemoglobin concentration can be rapidly assessed using point-of-care testing. Furthermore, as observed on the initial data set, three tiers of risk are discernible. The limitations of this scoring system are acknowledged. It has been specifically modelled on a unique data set and may not be applicable or show validity on external data.

CONCLUSION

To our knowledge, these are the first prospective data to evaluate comprehensively the main scoring instruments recommended for use in ruptured AAA repair. The GAS and Hardman Index do not perform as predictive instruments as well as previously reported. Furthermore, the V-POSSUM and RAAA-POSSUM also do not demonstrate compelling validity when applied to these data. The ERAS is an easily applied scoring system that allows patients to be quickly and accurately allocated to a low, medium, and high risk of perioperative death. It does not enable the prediction of surgical futility, however; further external assessment is required to confirm its validity.

AUTHOR CONTRIBUTIONS

Conception and design: AT, JM, RC
Analysis and interpretation: AT, JM, RC
Data collection: AT
Writing the article: AT, JM, RC
Critical revision of the article: AT, AL, JM, RC
Final approval of the article: AT, AL, JM, RC
Statistical analysis: AT
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